Gilded scars: decoding how metabolism and cancer cell-intrinsic features shape immunity in hepatocellular carcinoma

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Chapter 2

Macrophages and T cells in metabolic disorder-associated cancers

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Abstract

Cancer and metabolic disorders have emerged as major global health challenges, reaching epidemic levels in recent decades. Often viewed as separate issues, metabolic disorders are shown by mounting evidence to heighten cancer risk and incidence. The intricacies underlying this connection are still being unraveled and encompass a complex interplay between metabolites, cancer cells and immune cells within the tumour microenvironment (TME). Here, we outline the interplay between metabolic and immune cell dysfunction in the context of three highly prevalent metabolic disorders, namely obesity; two associated liver diseases, metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH); and type 2 diabetes. We focus primarily on macrophages and $CD8^+$ T cells, the critical roles of which in dictating inflammatory response and immune surveillance in metabolic disorder-associated cancers are widely reported. Moreover, considering the ever-increasing number of patients prescribed with metabolism disorder-altering drugs and diets in recent years, we discuss how these therapies modulate systemic and local immune phenotypes, consequently impacting cancer malignancy. Collectively, unraveling the determinants of metabolic disorder-associated immune landscape and their role in fueling cancer malignancy will provide a framework essential to therapeutically address these highly prevalent diseases.

Introduction

Metabolic disorders are metabolic dysfunction-associated medical conditions that have recently become one of the world's major health crises[1-3] (**Box 1**). These encompass three dominant metabolic disorders: obesity, metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH) (previously referred to as nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH)) and type 2 diabetes (T2D) (**Box 1**). The incidence of metabolic disorders has been steadily rising[4] due to a multitude of factors, ranging from an increasingly sedentary lifestyle, altered diets, and genetic predispositions[5-8] (**Fig. 1A**). However, their clinical needs remain largely unmet.

Alterations in metabolite composition at the cellular, local tissue and organism levels is a defining, yet underexplored, feature of metabolic disorders (**Fig. 1B**). In fact, patients presenting with metabolic disorders commonly exhibit alterations in lipids, sugars, and amino acids[9-19] (**Fig. 1B**). Compounded with caloric excess and nutrient imbalance inherent to most modern diets, metabolic dysfunction has far-reaching consequences in how energy is processed and utilized, and eventually leads to abnormalities in several biochemical processes disrupting normal health[5-7]. Indeed, metabolic disorders exacerbate the risk of cardiovascular and neurodegenerative diseases, the development of preneoplastic lesions (such as pancreatic intraepithelial neoplasias (PanINs)[20] and colorectal adenomas[21]) and numerous types of cancers, including hepatocellular carcinoma (HCC), pancreatic adenocarcinoma (PDAC) and colorectal cancer (CRC)[5,6,22,23] (**Box 1**). Metabolic disorders also modulate cancer therapy response, as exemplified by decreased chemotherapeutic efficacy[24] and the paradoxical increased response to immunotherapy in obese mice and patients living with obesity and cancer[25,26]. Strikingly, it is estimated that 3.6% of all globally diagnosed cancers in 2012 were linked to excess body weight alone[27], and that the number of cancer-related deaths linked to high body mass increased 35% worldwide between 2010 and 2019 (with liver cancer overwhelmingly contributing to these numbers)[28]. This overall highlight the need to uncover how tumorigenesis is shaped by metabolic disorder-associated metabolic derailment.

Cancer has long been viewed as a metabolic disease, with metabolic reprogramming currently recognized as a key requirement for cancer initiation and progression[29]. Because cancer cells can adjust their metabolic requirements when faced with cellular changes associated with the oncogenic process, as reviewed elsewhere[29,30], tumours are phenotypically responsive to alterations in the local nutrient availability in the tumour microenvironment (TME)[29]. Therefore, metabolic disorder-associated metabolite profile changes may also modulate oncogenesis (**Fig. 1C**) and thus constitute an underappreciated axis in cancer biology.

Among the cells involved in metabolic cooperation and competition within the TME are immune cells, including macrophages and T cells[31]. They have decisive roles in shaping tumour initiation, progression and dissemination by either facilitating or curbing the oncogenic process in a cell-dependent, organ-dependent and context-dependent manner[32]. Importantly, obesity, MASLD, MASH and T2D are associated with local and systemic immune dysfunction[33,34] (**Fig. 2**) and a chronic inflammatory state that drives several clinicopathological features of metabolic disorders[34], including insulin resistance. In fact, insulin resistance can be exacerbated by tumour necrosis factor (TNF), a pro-inflammatory cytokine produced by adipocytes in rodent mouse models of obesity and T2D[35]. Additionally, pro-inflammatory macrophages infiltrate the adipose tissue and are key drivers of

reduced insulin sensitivity in mouse models of obesity[36-38]. Critically, inflammation is a well-established driver of cancer initiation and progression[32]; thus metabolic disorder-associated immune alterations are a probable mechanism promoting increased tumorigenesis in patients with metabolic disorders. Metabolic disorder-associated alterations in metabolic and nutrient profiles tailor immune cell phenotypes and tumour-modulating properties and can also facilitate cancer dissemination, including metastasis to the liver[39-41] (**Box 2**). This thereby places immune-metabolic rewiring as a central process in fuelling malignancy in metabolic disorder-linked cancers.

In this Review, we focus on metabolic disorders arising from non-heritable factors, exploring the phenotypic adaptations, origin and tumour-modulating capabilities of macrophages and T cells in the context of obesity, MASLD, MASH and T2D. These metabolic disorders are often interconnected (**Box 1**). Of note, the preclinical studies discussed in this Review often utilize dietary-driven metabolic disorder and metabolic disorder-associated cancer models (see ref. 6 for examples of MASLD, MASH, and MASH-induced models of HCC, and ref. 42 for diet-induced obesity models). We further describe the influence of metabolites and nutrients on macrophage and T cell functions and their role in metabolic disorder pathogenesis and associated cancer development. We discuss potential links between these findings and what is currently known about the heterotypic communications between macrophages and T cells in metabolic disorder-associated cancers. We conclude by offering our perspective on how therapies originally aimed at treating metabolic disorders can alter macrophage and T cell functions, host systemic immunity, tumorigenesis, and limit or enhance the efficacy of anticancer treatments.

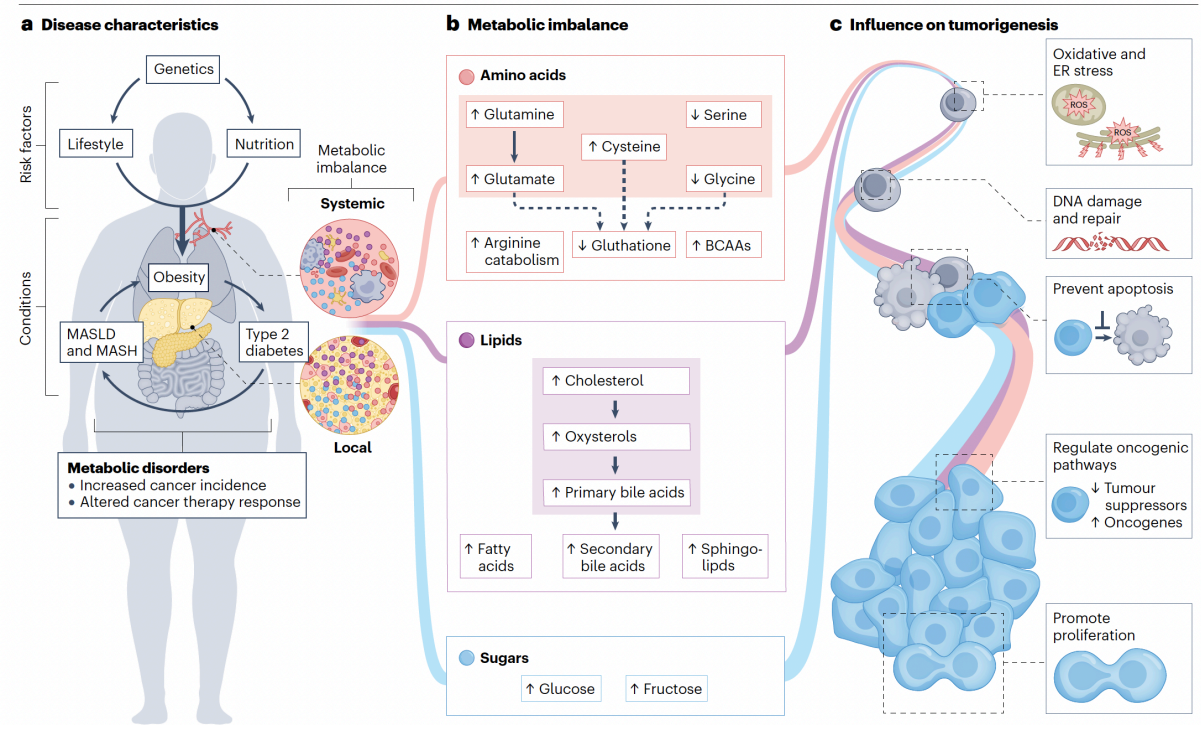

Fig. 1 | Metabolic disorders increase cancer development through metabolite imbalances. A. Patients with metabolic disorders are at increased risk of developing cancer. Risk factors underlying metabolic disorders include genetics, a sedentary lifestyle and excessive caloric intake. These can lead to obesity, metabolic dysfunction-associated steatotic liver disease (MASLD), metabolic dysfunction-associated steatohepatitis (MASH) and type 2 diabetes (T2D), which are often interconnected and have shared pathophysiological features, such as a systemic and local metabolite imbalance. Apart from their link with increased cancer incidence,

metabolic disorders also shape cancer therapy outcome by, for instance, boosting immunotherapy response while impairing chemotherapeutic efficacy in patients with obesity. **B.** Most metabolites, including amino acids (with the exception of glycine and serine), lipids and sugars (including dietary fructose) are increased in metabolic disorders. Amino acid imbalance may be involved in the reported reduced glutathione level in metabolic disorders[285]. Indeed, although glutamine, glutamate and cysteine are reportedly increased in metabolic disorders, serine and glycine levels are often low, which may constitute a limiting step in glutathione synthesis[286]. The list of altered metabolites is non-exhaustive and limited to those possessing well-known carcinogenic properties. The dashed arrows indicate correlated connections, whereas solid lines indicate direct and mechanistic connections. **C.** General pathways involved in tumourigenesis or tumour progression are fueled directly by metabolic imbalances. This can directly induce oxidative stress, endoplasmic reticulum (ER) stress[287] and downstream reactive oxygen species (ROS)[288], which can directly induce DNA damage (as observed on hepatocyte exposed to palmitate[289]) or impair DNA repair. Furthermore, metabolites can inhibit apoptotic pathways (for example, through exposure to increased levels of nitric oxide[290] which may be increased owing to heightened catabolism of arginine[286]) and alter oncogenic signalling pathways by inhibiting tumour suppressors or activating oncogenes (for example, associated with increased cholesteryl esters and oxidative stress accumulation, as seen in MASLD-induced hepatocellular carcinoma[291]). In addition, metabolites can directly promote proliferation of tumour cells in later stages of carcinogenesis (for example, increased fructose intake stimulates the production of microbiome-derived acetate that promotes cell proliferation and tumour growth[292]). Small arrows indicate either upregulation (upward arrows) or downregulation (downward arrows). BCAA, branched-chain amino acid.

Macrophages in metabolic disorders

Phenotypic plasticity of macrophages

Macrophages are professional phagocytic, innate immune cells that play an essential role in homeostatic biological processes, ranging from tissue repair, clearance of cellular debris, metabolic regulation, and immune surveillance through immune activation or immunosuppression[43,44].These wide-ranging functions showcase the immense plasticity of macrophages and underlie their capacity to respond to environmental cues and adapt their phenotype accordingly.

Macrophage phenotypic complexity has long been oversimplified into two extreme, dichotomic polarization states: the so-called ‘M1-like’, pro-inflammatory, anti-tumoral macrophages, and the wound-healing, pro-tumorigenic ‘M2-like’ counterpart. However, this nomenclature is likely reductionist, given the diverse phenotypes observed *in vivo*[45]. Nevertheless, invaluable information on macrophage phenotype and immune-metabolic features was obtained using these rather static definitions. For instance, wound-healing, anti-inflammatory macrophages typically exhibit higher CD36 expression, and favour fatty acid oxidation (FAO) and oxidative phosphorylation, whereas pro-inflammatory macrophages rely on glycolysis[46]. To account for their diverse phenotypes, an inflammatory axis was proposed, orthogonally to a metabolic axis, which comprises the changes undergone in macrophages within nutrient-enriched or scarce conditions, thereby co-existing in distinct niches within the TME[45].

Similarly, macrophages possess distinct phenotypes in metabolic disorders (**Fig. 2A**). In metabolic dysfunction concomitant to obesity in high-fat diet (HFD)-fed mice, adipose tissue macrophages can exhibit a distinct ‘metabolically activated’ phenotype in response to palmitate, a saturated fatty acid (SFA), displaying features common to two inflammatory states, including the overexpression of pro-inflammatory cytokines yet high levels of CD36 (involved in lipid uptake) and

cholesterol efflux transporter, ATP-binding cassette transporter A1 (ABCA1) (ref. 47). A Toll-like receptor 4 (TLR4)-induced, free fatty acid (FFA)-mediated metabolic phenotype with dampened response to acute liver injury was also observed in myeloid cells and macrophages in the bone marrow and liver of obesity-associated MASH in Western diet-fed mice[48]. Triggering receptor expressed on myeloid cells (TREM2)$^+$ macrophages, a subset of lipid-associated macrophages (LAMs), were recently identified in several organs and pathological states, including in patients living with obesity, HFD-fed mice[49] and in MASLD and MASH mice[50]**.** In HFD-fed mice, TREM2$^+$ LAMs limit adipocyte hypertrophy and prevent hypercholesterolaemia and glucose intolerance in a TREM2-dependent manner[49]. In MASLD-induced, HFD-fed or Western diet-fed mice, TREM2 expression was upregulated in macrophages via hepatocyte-derived sphingosine-1 phosphate (S1P), subsequently mediating clearance of dying steatotic hepatocytes through efferocytosis and, thus, preventing overt inflammation[50]. As will discussed later, TREM2$^+$ macrophages are largely associated with a detrimental role in established tumours[51,52], overall highlighting that context matters when assessing macrophage phenotypic diversity.

Macrophages in metabolic disorders can be organized in crown-like structures (CLSs), where macrophages infiltrate areas with dying, hypertrophic adipocytes[53]. These structures are observed in adipose tissue sites in patients living with obesity and in mouse models of genetic-induced and diet-induced obesity (such as leptin-deficient ob/ob and HFD-fed mice)[38,54]. They also closely associated with lipid-laden hepatocytes in humans and mice with MASLD and MASH[55]. CLSs are also detected in fat deposits in cancerous tissues of patients with breast cancer[53]. Within these structures, macrophages are essential in clearing dying adipocytes, collecting cellular debris and scavenging lipids. These processes can modulate their phenotype and elicit their activation via pattern recognition receptors, such as nucleotide-binding oligomerization domain (NOD) or TLR signalling pathways, and lead to activation of nuclear factor κB (NF-κB), promoting a pro-inflammatory cascade and contributing to systemic insulin resistance[36,53].

Macrophage ontogeny

In homeostasis, tissue-resident macrophages can be derived from embryonic precursors capable of self-renewal, or via local differentiation of blood-derived monocytes[56]. This balance is shifted towards an increase in monocyte-derived cells during tissue injury[44], metabolic disorders[49,57,58] and cancers[43,59,60] (**Fig. 2A**), yet its implications on macrophage phenotype are still being investigated. For instance, in HFD-fed mice, macrophages populating adipose tissue are estimated to be mostly monocyte-derived, wherein they display a more pro-inflammatory phenotype and can increase monocyte production in the bone marrow[58]. These probably include TREM2$^+$ macrophages, which are largely derived from circulating monocytes in HFD-fed mice[49]. Still, adipose tissue-resident macrophages can also undergo self-renewal in obesity-associated inflammation[61], suggesting that sustained infiltration of blood-derived monocytes is not the sole contributor to the macrophage pool. In pancreatic islets, macrophages are maintained by self-renewal independent from blood-circulating monocytes[62]. To our knowledge, whether this balance is altered in T2D still remains to be fully established.

In MASLD and MASH, recent reports suggest that most tissue-resident Kupffer cells in the steatotic liver are derived from monocytes. In HFD-fed mice, macrophages lose T cell immunoglobulin and mucin domain containing 4 (TIM4) expression, a marker for tissue-resident macrophages, and increase expression of lipid-associated genes, including TREM2 (ref. 57). Monocyte-derived Kupffer

cells can exacerbate liver damage in MASH, are more inflammatory, and are less efficient than embryonic-derived Kupffer cells in coping with lipid overload and in assisting hepatocyte lipid storage[63]. Albeit local proliferation of embryonic-derived macrophage still occurs in the context of MASH, their self-renewal capacity and survival are compromised possibly through accumulation of endoplasmic reticulum (ER) stress and oxidative stress in MASH[63]. In fact, Kupffer cells in methionine-deficient and choline-deficient diet (MCD)-driven and HFD-driven mouse models of MASLD and MASH exhibit increased expression of neutrophil cytosolic factor 1 (NCF1), a protein driving reactive oxygen species (ROS) production in myeloid cells[64]. NCF1 can be induced by palmitate exposure and it promotes iron accumulation through crosstalk with hepatocytes, lipid peroxidation and consequent ferroptosis of Kupffer cells[64], therefore partially explaining their impaired renewal potential and subsequent infiltration of monocyte-derived macrophages in MASLD and MASH.

Importantly, metabolic changes common to metabolic disorders have far-reaching influence on systemic immunity. Hyperglycaemia promotes bone marrow myelopoiesis and increases the number of circulating monocytes[65]. High cholesterol can prime hematopoietic stem cells to differentiate into inflammatory monocytes[66]. These findings suggest a metabolite-dependent mechanism responsible for the increase of macrophage progenitors in metabolic disorders.

Metabolites underlying pro-inflammatory macrophage skewing

Macrophages adapt to metabolite changes in their surrounding milieu[43], suggesting that metabolic disorder-associated metabolite alterations can modulate their abundance and phenotype (**Fig. 2A-C**). C-Chemokine C-C motif ligand 2 (CCL2), a monocyte-attracting chemokine that induces macrophage infiltration into adipose tissues in genetic-induced and diet-induced mouse models of obesity, is increased in adipocytes and correlates with metabolic disorder pathological markers, including serum triglyceride levels[67]. High expression of very-low-density-lipoprotein receptor (VLDLR) in CLS-associated macrophages in adipose tissues promotes lipid uptake to induce macrophage expression of *Ccl2*, interleukin-1β (*Il1b*) and *Tnf*, exacerbating adipose tissue inflammation, insulin resistance and glucose intolerance in obese mice[68].

In mouse models of hypercholesterolaemia, uptake of oxidized phospholipids drives a pro-inflammatory phenotype in macrophages, sustaining systemic inflammation and possibly exacerbating other metabolic disorders, including MASH[69]. In the MASLD liver, polyunsaturated fatty acid**s** (PUFAs) and SFAs distinctly influence macrophage polarization states. Indeed, in HFD-fed diet mice, Kupffer cells exhibited upregulation of inflammatory genes, such as *Tnf*, *Il6* and *Il1b*. *Ex vivo* treatment of Kupffer cells with PUFAs induced a reparative phenotype, whereas higher SFAs levels promoted a pro-inflammatory state in a NF-κB-dependent manner, with increased expression of *Tnf* and *Il6* (ref. 70), suggesting that fatty acid species matter in the context of macrophage activation.

In adipose tissue of obese patients and in HFD-fed mice, glutamine levels are reduced (**Fig. 1B**) owing to lower glutamine synthetase expression, an enzyme crucial for glutamine synthesis[19]. Low glutamine synthetase expression is associated with a pro-inflammatory signature, including IL-6, IL-1β and TNF, within adipose tissue[19]. Glutamine supplementation in HFD-fed mice reduced *Ccl2* expression and the proportion of $CD11c^+$ macrophages accumulating in adipose tissue, while also attenuating adipose tissue human macrophage *IL1B* and *IL6* expression *in vitro*[19]. This suggests a role for glutamine in modulating macrophage polarization in metabolic disorders[19].

Macrophage-mediated modulation of MASLD-to-MASH transition

In the MASLD liver, hepatic macrophages are exposed to a plethora of signals that can drive their activation to promote disease aggravation and progression to MASH (**Fig. 2D**)[71]. Their engagement can occur, for instance, following exposure to damage-associated molecular patterns (DAMPs) released from damaged hepatocytes, and via TLR-mediated recognition of microbiome-derived endotoxins, owing to the compromised gut barrier that is common in patients with MASLD and MASH[71]. Local macrophage activation in MASLD also ensues the engulfment of dying steatotic hepatocytes containing lipid droplets with cholesterol crystals, as was observed in cholesterol-supplemented, HFD-fed mice, leading to inflammasome activation and IL-1β release[72]. Once activated, pro-inflammatory macrophages contribute to ROS release, stellate cell activation and fibrosis accumulation, thereby supporting the transition to MASH[6,71] — a disease in which ROS-fighting glutathione levels are already low[9]. Indeed, oxidative stress-associated Kupffer cell ferroptosis was shown to drive MASH features in MCD-fed mice, and ferroptosis blockade ameliorated *hepatic* steatosis**,** inflammation and liver damage in this setting[64].

Excessive hyper nutrition and the associated consequence of promoting obesity further contribute to the inflammatory cascade linking MASLD-to-MASH transition by disrupting $TREM2^+$ macrophages. In this context of sustained nutrient overload, necrotic hepatocyte-derived DAMPs induce hepatic TNF and IL-1β secretion to shed macrophage TREM2 receptor, preventing efferocytosis-mediated clearance of dying cells and licensing the progression to MASH[50]. Concurrently, levels of circulating soluble TREM2 can predict MASH severity in mice and humans, and *Trem2*-deficient macrophages were also shown to display defective lipid handling and to exacerbate local fibrosis and cell death in MASH[73]. These reports highlight that inflammatory cues and dietary nutrient exposure alter macrophage function to ultimately regulate MASLD-to-MASH evolution.

Macrophage-mediated modulation of T2D pathogenesis

Macrophages are one of the most abundant cells in the pancreatic islets of patients with and mouse models of T2D[74], where they promote beta cell dysfunction, insulin resistance through TNF and IL-1β, and local pancreatic inflammation (**Fig. 2E**)[75]. This process is likely exacerbated in dyslipidaemia, because palmitate can induce beta cell-mediated recruitment of macrophages[76] and macrophage-derived IL-1β secretion[77]. This may also occur indirectly via palmitate-induced metabolic reprogramming of macrophages, consequently exacerbating pro-inflammatory cytokine secretion[78]. Macrophages residing the pancreatic islets can also be activated by amyloid polypeptide accumulation, a common trait observed in T2D, leading to IL-1β secretion and beta cell dysfunction in obese mice [79], overall positioning macrophages as central mediators of T2D pathogenic features.

Macrophages in metabolic disorder-associated cancers

Macrophages shape tumorigenesis through metabolic regulation

Growing evidence suggests the emergence of LAMs in metabolic disorders and cancer, where they play a major role in disease initiation and progression[80]. Importantly, their formation relies at least partially on exposure to metabolites, particularly lipids[80]. In patients with breast cancer, LAMs are associated with worse prognosis[81]. In prostate cancer-bearing mice, a HFD was shown to drive LAM formation[82]. In this context, cancer cell-derived IL-1β promoted tumour-associated macrophage (TAM)

macrophage receptor with collagenous structure (MARCO) expression, leading to MARCO-driven uptake of low-density-lipoproteins (LDLs), downstream secretion of chemokine C-C motif 6 (CCL6) and promotion of cancer cell migration[82]. MARCO blockade hindered tumour growth and invasion[82]. Another report shows that TAMs in melanoma-bearing mice have high lipid content and increased ER stress[83]. In this melanoma model, administration of liver X receptor α (LXRα) agonist promoted lysophosphatidylcholine acyltransferase 3 (LPCAT3) expression, consequently hampering macrophage lipid accumulation and survival, and reducing tumour growth[83]. Whether these macrophages share features with LAMs was not explored in this study, although it is probable that they do, given the reported increased lipid build-up in these cells[83]. Interestingly, fatty acid binding protein 4 (FABP4), a regulator of lipid uptake and metabolism, is increased in adipose tissue, including macrophages, of patients with breast cancer and obesity[84]. FABP4 binding to FFAs can promote macrophage NF-κB activation and consequent IL-6 release, fuelling breast cancer progression in mice[84]. Crucially, FABP4 is also implicated in driving macrophage cholesterol accumulation, and macrophage-specific *Fabp4* deletion led to a reduction of inflammatory cytokine secretion (including TNF and IL-1β) in a mouse model of atherosclerosis[85]. Because FABP4 is part of the TREM2$^+$ LAM signature identified in obesity[49], its cancer-promoting roles may also encompass its known detrimental interactions with T cells, as will be discussed later.

HFD-fed, CRC-bearing obese mice were recently shown to harbour increased expression of programmed cell death protein 1 (PD-1) in TAMs with reduced phagocytic capacity and increased lipid uptake[26]. PD-1 binding was also shown to suppress TAM glycolytic activity, and PD-1 blockade restored phagocytosis and glycolysis and induced expression of inducible nitric oxide synthase (iNOS)[26], potentially conferring a tumour-suppressing capacity to these TAMs. This report suggests that obesity-associated lipid deregulation and inflammation can fuel the emergence of PD-1$^+$ TAMs, which were elicited after administration of HFD in mice and the onset of metabolic dysfunction[26].

In other reports, HFD-fed mice exhibited increased secondary bile acid deoxycholic acid (DCA) production, which was shown to promote pro-inflammatory macrophages in a TLR2-dependent manner[86]. Conversely, the secondary bile acid litocholic acid (LCA) can inhibit inflammation in HFD-fed mice by inactivating the inflammasome and thus IL-1β cleavage through binding to Takeda G protein-coupled receptor 5 (TGR5) on macrophages[87]. Therefore, these studies suggest that distinct bile acids impact macrophage polarization in various ways. TGR5 activation was also shown to induce IL-10 on intestinal macrophages in a mouse model of colitis[88], a cytokine which is mostly counterproductive once tumours are established given its immunosuppressive capabilities[89]. The net effect of dietary fat-induced bile acid production in metabolic disorder-associated cancers remains to be fully investigated.

Notably, macrophage-derived metabolites can shape the local environment to become more tumour-promoting and further fuel an inflammatory landscape. For instance, macrophages can increase local oxidative stress, as evident in an HFD-induced mouse model of MASLD, wherein monocyte-derived macrophages secrete ROS in response to palmitate[90]. In hypercholesterolaemic mouse models of breast cancer, 27-hydroxycholesterol (27-HE) levels are increased and facilitate oestrogen receptor-mediated tumour growth in mouse models of breast cancer[91]. In these models, macrophages were shown to express cytochrome p450 family 27 subfamily A members 1 (CYP27A1), an enzyme that catalyses 27-HE production from cholesterol. This was shown to sustain breast cancer cell proliferation *in vitro* in a CYP27A1-dependent manner[91]. 27-HE can, in turn, bind to oestrogen receptors expressed on macrophages themselves and induce the expression of pro-inflammatory genes *Tnf*, *Il1b* and *Il*6 (ref. 92).

Macrophages in MASH-induced HCC

Macrophage-fuelled inflammation has been posited as a critical node in MASH-induced HCC (**Fig. 2D**), with contributions from pro-inflammatory cytokines, including IL-1β and especially TNF[6]. For instance, in a mouse model of MASH (major urinary protein-urokinase-type plasminogen activator (*MUP-UpA*)), a HFD promoted an increase in hepatic immune cell infiltration, liver damage, oxidative stress, and ER stress in hepatocytes. These factors, in turn, elicited macrophage-derived TNF secretion, an inflammatory cytokine essential to drive both MASH and its transition to HCC[93,94]. This inflammatory axis is probably exacerbated in the lipid-enriched environment of MASH, as FFAs stimulate hepatic macrophage TNF secretion, leading to lipid droplets accumulation in hepatocytes[95]. In MASH-bearing, *MUP-UpA* mice, a high-fructose diet induced ER stress in intestinal epithelial cells, consequently promoting gut barrier deterioration and causing bacterial translocation to the liver and activation of TLR4 on hepatic macrophages[96]. TLR4 engagement triggered TNF production in this context, and therefore, increased hepatocyte *de novo* lipogenesis, MASH worsening, and HCC promotion[96]. Fructose was also shown to induce IL-1β secretion in monocytes and macrophages *in vitro* by heightening their response to endotoxins[97], which could fuel local cancer-promoting inflammation. In line with the observations linking TNF and ER stress to MASH-to-cancer progression, recent reports suggest that ER stress-targeting and TNF-targeting strategies are promising therapeutic avenues in mice and patients with MASH and MASH-induced HCC[98,99].

In choline-deficient-HFD (CD-HFD)-fed mice, which show concomitant signs of increased adipose tissue and body mass additional to hepatic alterations, consequent MASH-induced HCC development was accompanied by progressive accumulation of pro-inflammatory, monocyte-derived TAMs[100]. In parallel, MASH-induced HCC in CD-HFD-fed mice display an enrichment of macrophages expressing fatty acid-binding protein 5 (FABP5), a lipid metabolism protein associated with LAM formation and immunosuppression[100], further highlighting the dynamic phenotypic changes of TAMs during cancer outgrowth. FABP5 inhibition led to cancer cell ferroptosis through lipid peroxidation and to the accumulation of inflammatory, immune-activating macrophages, altogether curbing HCC progression[100] and, thus, supporting an anti-tumorigenic role for pro-inflammatory macrophages in this context.

Despite the recent advances herein described, the definitive role of macrophages in MASH-to-HCC evolution requires further investigation and must be considered in light of the ever-increasing appreciation of TAM heterogeneity. Furthermore, the influence of macrophage ontogeny in the context of MASH-to-HCC development calls for further consideration of their relative roles in liver diseases preceding HCC. Importantly, this extends beyond the liver and to different cancer types in which the influence of macrophage ontogeny in tumour-promoting processes is still being elucidated[43,44,101].

Macrophages in T2D-associated PDAC

Despite T2D being associated with increased PDAC incidence[23], the mechanisms underlying this interconnection remain poorly understood. However, it is well-established that PDAC development is fuelled by macrophage-associated inflammation[59,102,103], suggesting that islet macrophage pro-inflammatory polarization observed in T2D[34,79] may trigger the oncogenic potential of pancreatic epithelial cells.

In KPC mice ($Kras^{G12D/+}$; $Trp53^{R172H/+}$; P48-Cre; a genetically engineered mouse model of PDAC), monocyte-derived IL-1β$^+$ TAMs, elicited partially through cancer cell-derived TNF, maintain a chronic inflammatory environment to sustain PDAC cell proliferation and survival[103]. An IL-1β-response signature was also observed in a mouse model of pancreatitis and in PanIN lesions preceding PDAC in mice and human patients, suggesting that IL-1β may also support the transition from PanIN to PDAC[103]. Crucially, macrophage-derived TNF, a cytokine that is elicited through IL-1 signalling, is necessary for the induction of an NF-κB-driven acinar-to-ductal metaplasia, an early step of pancreatic carcinogenesis, in a mouse model of pancreatitis[102]. While such mechanisms underlying macrophage functions have not been studied in the context of metabolic disorders, these findings suggest that T2D-associated islet macrophages, which are pro-inflammatory and secrete IL-1β[34,77], can potentially contribute to PDAC development (**Fig. 2E**). Furthermore, considering that the levels of systemic, adipocyte-derived TNF are increased in mouse models of obesity and T2D, and that macrophages themselves are a major source of TNF in the context of obesity and insulin resistance[35,38], the role of IL-1β$^+$ macrophages may be particularly important in obesity-associated T2D.

Moreover, correlative data suggests that the IL-1β-mediated, macrophage-mediated tumour-promoting axis may be further fuelled by prostaglandin, a physiologically active lipid that promotes pancreatic fibrosis[104], immunosuppression[105], and PDAC invasion[106], and cooperates with TNF to induce IL-1β$^+$ TAM reprogramming in PDAC[103]. In fact, macrophages themselves can secrete prostaglandin, which may be modulated through T2D-associated metabolic changes. For instance, lipid droplet accumulation in macrophages leads to prostaglandin secretion[107]. This also occurs upon exposure to the lipid components palmitate and oxidized LDL (oxLDL)[108,109]. Indeed, palmitate was shown to induce cyclooxygenase-2 and consequent prostaglandin secretion in macrophages from diabetic-obese db/db mice[108], whereas oxLDL fosters oxidative stress and prostaglandin production in human macrophages *in vitro*[109]. Therefore, a possible interplay between macrophage-derived prostaglandin and IL-1β to exacerbate pancreatic disease and PDAC development might be further heightened in the context of dyslipidaemia, which is typically seen in patients with T2D[110]. Altogether, the connection between macrophages, T2D and PDAC development is multifaceted and is still being deciphered (**Fig. 2E**).

T cell subsets in metabolic disorders

The number and phenotype of T cells, indispensable players in the adaptive immunity arm, are altered in metabolic disorders[34,111], supporting their disease-modulating properties and alluding to their role in influencing metabolic disorder-associated cancer development.

In patients living with obesity and mouse models of diet-induced obesity, T cells exhibit signs of exhaustion and dysfunction[25] (**Fig. 2B, C**). In obesity, C-X-C chemokine receptor type 3 $(CXCR3)^+$ effector memory $CD4^+$ T cells, which are induced by dietary palmitate overexposure, exhibit a pro-inflammatory phenotype, infiltrate inflamed adipose tissue in HFD-fed mice, and are systemically increased in patients with obesity, supporting their role in contributing to obesity-associated inflammation[112]. Obese-associated adipose tissues also harbour exhausted T cells and less regulatory T cells (T_{reg}) (see **Table 1**), even after weight loss[113]. Reduction in T_{reg} cell numbers was suggested to be associated with a possible lower peroxisome proliferator-activated receptor γ signalling (PPARγ) and consequently reduced proliferative capacity of these cells[113]. In adipose tissue of ob/ob mice and HFD-fed mice, a reduction in $CD4^+$ T cells and T_{reg} cells was observed[114], although the mechanism underlying this regulation was not explored. In contrast, $CD8^+$ T cells were more abundant and were required for adipose tissue inflammation by fostering macrophage infiltration and macrophage-derived TNF production, consequently promoting insulin resistance[114]. This highlights a T cell-orchestrated, macrophage-dependent detrimental effect that could fuel inflammation-mediated malignancies.

Distinct subsets of $CD4^+$ T cells are involved in MASLD and MASH pathogenesis, with further contribution from macrophages and inflammation in this process. For instance, $CD4^+$ T helper 1 (T_H1) cells responding to oxidative stress-associated antigens can exacerbate MASH development by eliciting the activation of pro-inflammatory macrophages[115]. Similarly, glycolysis-dependent, $CXCR3^+$ $CD4^+$ T helper 17 (*T_H17 cell*) abundance is increased in the liver of patients living with obesity and with MASLD or MASH, and in the liver of obesity-associated mouse models of MASLD and MASH, where they contribute to MASLD and MASH pathologies through the release of pro-inflammatory cytokines and the promotion of macrophage infiltration[116]. In parallel, patients with MASLD and MASH and the preclinical mouse models of both diseases often display increased hepatic and systemic $CD8^+$ T cells[117,118].

Distinct T cell subsets are also expanded in T2D and contribute to T2D-associated inflammation. Specifically, the number of T_H17 cells and their inflammatory capacity are systemically increased in patients with T2D living with obesity as a comorbidity, compared to healthy subjects[119], which could suggest a T_H17 role in modulating T2D pathogenesis (**Fig. 2E**). In patients with T2D, T_H17 cells exhibit decreased mitochondrial mass, indicating a preference for glycolysis as an energy source. However, blocking FAO, but not glycolysis, was sufficient to drive T_H17-mediated secretion of pro-inflammatory cytokines[120]. This reliance on lipid metabolism suggests that increased circulating FFAs might sustain T_H17-driven T2D inflammation even during proper glycaemic control[120]. T2D-associated excess glucose may also contribute to immune impairment and inflammation by negatively modulating T cell function. Indeed, patients with T2D exhibit increased numbers of senescent $CD4^+$ and $CD8^+$ T cells with impaired migratory capacity and lower glucose uptake[121] and, in obese mice with T2D, hyperglycaemia, not insulin, was shown to curb memory $CD8^+$ T cell cytokine production and anti-tumour response following injection of melanoma cells[122]. Furthermore, T cells in hyperglycaemic mice produce higher levels of pro-inflammatory cytokines, including IL-17 (ref. 123).

Overall, these reports suggest that metabolic disorders have a profound impact on T cell function at the local and systemic levels, probably shaping the host susceptibility to cancer development through T cell dysfunction, reduced immunosurveillance and/or T cell-driven inflammatory capacity.

T cells in metabolic disorders-associated cancers

Metabolite shaping of T cell function

T cells undergo a vast metabolic reprogramming upon activation, including increasing aerobic glycolysis and amino acid or lipid uptake to sustain their rapid proliferation and effector functions. These changes make them particularly susceptible to variations in the metabolic profile of their surrounding milieu[111] (**Fig. 2B, C**). Considering the metabolite shift taking place in metabolic disorders (**Fig. 1B**), it is expected that individual metabolites and metabolic challenges can regulate T cell states (**Fig. 2B, C**) that subsequently impact oncogenesis.

For instance, amino acids are essential to foster T cell activity and anti-tumour capacity[124], suggesting that metabolic disorder-associated amino acid imbalance can modulate their function (**Fig. 1B**). This includes glutamine, which has a major role in supporting T cell effector functions by promoting mammalian target of rapamycin complex 1 (mTORC1) activation and glutathione synthesis to cope with ROS, for instance[124]. In fact, obese, HFD-fed mice exhibit low systemic glutamine levels, and the effector function of $CD8^+$ T cells is impaired in HFD-fed, CRC-bearing mice[125]. Glutamine is a substrate for L-type amino acid transporter 1 (LAT-1), an amino acid transporter critical to sustain T cell activity[125]. In line with this, glutamine supplementation rescued proliferation and effector function, such as interferon-γ (IFNγ) production, in splenic $CD8^+$ T cells extracted from these mice[125]. Moreover, serine was shown to support one-carbon metabolism in T cells and to foster their effector program and proliferative capacity *in vitro* and *in vivo*[126], wherein mice fed a serine and glycine-deficient diet had lower antigen-specific, splenic T cell expansion upon challenge with bacterial infection[126]. Glycine supplementation, which can be converted into serine, was shown to rescue serine-deprived T cell effector function in this context[126]. Therefore, the low levels of both serine[18,127] and glycine[128] seen in patients with metabolic disorders (**Fig. 1B**) might further contribute to T cell dysfunction in metabolic disorder-associated cancers.

T cell activity and differentiation can also be modulated by lipids. In a mouse model of melanoma lung metastasis, excessive intratumoural cholesterol led to its accumulation in intratumoural $CD8^+$ T cells, promoting ER stress and consequent upregulation of immune checkpoint molecules, curbing their anti-tumour potential[129]. A similar finding was observed in CRC-inoculated mice, where cancer cell-derived fibroblast growth factor 21 (FGF21), a hormone with metabolic-modulating properties, induced cholesterol accumulation in intratumoural $CD8^+$ T cells by promoting cholesterol biosynthesis, resulting in dampened cytotoxicity and anti-tumour function[130]. Contrastingly, cholesterol deficiency in T cells driven by cholesterol depletion in the TME or through enforcing T cell cholesterol efflux was shown to hinder T cell proliferation and to promote autophagy-induced apoptosis[131]. $CD8^+$ T cells exhibited decreased proliferation compared to $CD4^+$ T cells in this context, suggesting a higher cholesterol dependency for $CD8^+$ T cells[131]. Interestingly, memory T cells, which are increased in obese mice and critical in driving anti-tumour response in the context of anti-PD1 therapy[25], rely on FAO for their differentiation, survival and respiratory capacity[132], suggesting that alterations in lipid availability may influence the differentiation and maintenance of this T cell subset. Overall, whether metabolic

disorder-associated hypercholesterolaemia and dyslipidaemia can modulate T cell dysfunction in metabolic disorder-associated cancers remains to be established.

The influence of lipids on T cell regulation is further complicated by the co-occurrence of oxidative stress. For instance, lysophosphatidic acid (LPA), a phospholipid found to be increased in patients with cancer, obesity or insulin resistance[133], induced activation of LPA receptor (LPAR), promoting FAO and increased intracellular ROS levels in $CD8^+$ T cells[134]. This metabolic shift triggered an exhaustion phenotype in $CD8^+$ T cells and dampened cytotoxicity, hindering anti-tumoral T cell function towards melanoma cells[134]. Comparably, CD36-mediated oxLDL uptake by $CD8^+$ T cells promoted progressive T cell dysfunction through p38 activation and increased lipid peroxidation. This state is reversed upon glutathione peroxidase 4 (*Gpx4*) overexpression, decreasing oxidative stress and increasing secretion of effector cytokines, and promoting anti-tumour function in melanoma-bearing mice[135]. Importantly, terminally exhausted T cells display increased oxidative stress owing to mitochondrial dysfunction[136], suggesting that overexposure to lipids may exacerbate an exhausted phenotype through oxidative stress.

Importantly, metabolic disorders can modulate how cancer cells utilize lipids, therefore, impacting neighbouring T cells. In a HFD-fed mouse with subcutaneous colon cancer, $CD8^+$ T cell activity was impaired due to obesity-associated tumour metabolic remodelling, where tumour cells increase FFA usage to sustain their growth, leading to FFA deprivation in the TME and consequently dampening $CD8^+$ T cells infiltration and anti-tumour function[137]. This finding highlights that FFAs are critical to sustain the metabolic activity and effector function of activated $CD8^+$ T cells, exposing their vulnerability to metabolic alterations in the TME[137].

T cell in MASH-induced HCC

Hepatic and systemic $CD8^+$ T cells are more abundant in patients with and preclinical models of MASH and MASH-induced HCC[117,118], where they have major, and often detrimental, roles during disease progression[33] (**Fig. 2D**). Amongst these are auto-aggressive $CXCR6^+$ $CD8^+$ T cells, a subset that promotes TNF-dependent hepatocyte killing in CD-HFD-fed mice exhibiting MASH, triggering local inflammation and, thus, possibly increasing susceptibility to liver cancer development[138]. Interestingly, TNF release and granzyme B expression were dependent on high levels of acetate, which was hypothesized to be released upon hepatocyte exposure to FFAs or secreted by the microbiome[138]. Orthogonally, MASH-HCC preclinical models and patients have been recently reported to be refractory to T cell-centric immunotherapy[118]. This effect was associated with the expansion of the $CXCR6^+$ $PD\text{-}1^+$ $CD8^+$ T cell subset, which promoted increased tumour burden and shortened survival, overall indicating a detrimental role for this particular T cell subtype in MASH-induced HCC[118]. However, in the *MUP-UpA* MASH-induced HCC mouse model, $CD8^+$ T cell depletion accelerated HCC outgrowth[139], suggesting $CD8^+$ T cells can also be beneficial in curtailing MASH-induced HCC progression.

Interestingly, reduced content of $CD4^+$ T cells in MCD-fed, liver-specific *Myc*-overexpressing mice fuelled HCC[140], highlighting a beneficial role for $CD4^+$ T cells in MASH-induced HCC. $CD4^+$ T cells are more susceptible to cell death through oxidative stress owing to their elevated mitochondrial mass, and exposure to linoleic acid (a PUFA that is increased in MASLD and MASH) induced their selective death through ROS generation[140].

Together these findings suggest that the influence of $CD8^+$ T cells on MASH-induced HCC is context- and subtype-dependent, while $CD4^+$ T cells exhibit an anti-tumour phenotype. Whether

MASH-associated metabolites have roles in these processes and what these roles are remain to be fully explored.

T cells in T2D-associated PDAC

In PDAC, the infiltration pattern of T cells is heterogeneous across patients. High $CD8^+$ T cell abundance and proximity to tumour cells is associated with better patient prognosis[141,142]. In the lipid-enriched PDAC environment, accumulation of long-chain fatty acids (such as palmitate) in $CD36^+$ T cells impaired mitochondrial function, induced lipotoxicity and consequently promoted T cell dysfunction in the KC ($Kras^{G12D/+}$; P48-Cre) mouse model[143] (**Fig. 2E**). This process already takes place in early PanIN lesions, suggesting its importance in cancer initiation[143]. Whether T2D-associated dyslipidaemia or comorbid pancreatic fat accumulation accelerate this process should, therefore, be assessed.

Despite $CD8^+$ T cells exerting beneficial effects in pancreatic cancer[141,142], specific T cell subsets may also accelerate PDAC development. This is particularly evident for IL-17-producing T cells, such as $CD4^+$ T_H17 cells, which are elevated in the circulation of patients with T2D [119]. IL-17 promotes PanIN initiation and progression[144], as well as PDAC malignant outgrowth subsequent to chronic pancreatitis[145] (**Fig. 2E**). Similarly, in a mouse model of PDAC overexpressing ovalbumin antigen (OVA), OVA-specific $CD4^+$ T_H17 cells are enhanced and govern an early pathological response driving fibrosis and PDAC progression from PanIN lesions[146]. Moreover, in patients with PDAC and in PDAC preclinical models, intratumoural IL-17-producing T cell content is increased[147]. T_H17 cells sustain dual oxidase 2 (DUOX2) expression on PDAC cells, an enzyme that has been associated with ROS production, leading to increased PDAC tumorigenesis and worse prognosis in patients with PDAC[147]. Overall, these findings provide correlative data connecting PDAC development and T2D through IL-17-producing, pro-inflammatory $CD4^+$ T_H17 subsets (**Fig. 2E**).

Similarly to MASH-induced HCC, a dichotomic role of $CD8^+$ T cells is also observed in PDAC, with disease-promoting and disease-limiting phenotypes in a context-dependent and subtype-dependent fashion. Indeed, although $CD8^+$ T cells are largely associated with better prognosis in PDAC[141,142], a novel subset of IL-17^+ $CD8^+$ T cells was recently shown to accelerate PDAC progression through pro-fibrotic crosstalk between fibroblasts, cancer cells and T cells in mice inoculated with PDAC cells[148]. It remains to be established whether IL-17^+ $CD8^+$ T cells are also observed in T2D, where IL-17-producing $CD4^+$ T cells are increased[119], and whether this figures as an additional mechanism underlying T2D-associated pancreatic carcinogenesis.

Macrophage–T cell crosstalk

The abundance, phenotype and oncogenic potential of several immune cells are altered in metabolic disorders (**Table 1**). Perhaps the most studied among these are the heterotypic interactions between macrophages and T cells, which hold implications for the modulation of metabolic disorder-associated cancers.

Once tumours are established, macrophages with an immunosuppressive and tumour-permissive phenotype can modulate tumour progression by hindering the anti-tumour function of T cells[43] (**Fig. 2B, C**). This can occur through the expression of immune checkpoint molecules or metabolic competition. For example, lactate can influence macrophage polarization towards a regenerative phenotype and induce macrophage programmed death-ligand 1 (PD-L1) expression[149], which can inhibit T cell activity by binding to PD-1. Kynurenine, a tryptophan metabolite increased in

obesity[150], upregulates CD39 expression on TAMs, which can inhibit T cells through adenosine production[151], a metabolite with immunosuppressive properties[152]. Albeit these reports are not in metabolic diseases, these metabolites are altered in such disorders and, thus, probably influence macrophage function and crosstalk with T cells.

In obese, HFD-fed, CRC-bearing mice, TAMs express PD-1, which is hypothesized to be driven by exposure to obesity-associated metabolites, including palmitate[26]. PD-1 activation in TAMs curbs their co-stimulatory capacity, such that PD-1 blockade or myeloid-specific PD-1 deletion improves their antigen-presenting cell capacity to boost anti-tumour $CD8^+$ T cell activity[26]. In CD-HFD-fed, MASH-induced HCC-bearing mice, FABP5 inhibition promoted expansion of pro-inflammatory TAMs with co-stimulatory capacity, increasing $CD8^+$ T cell proliferation and cytotoxicity[100]. Together, these findings suggest that therapeutically modulating macrophage subsets could boost anti-tumour immunity in metabolic disorder-associated cancers.

$TREM2^+$ TAMs curb T cell-mediated anti-tumour response by promoting immunosuppression and resistance to immunotherapy[51,52]. *Trem2*-deficient mice are refractory to many cancer types, including CRC and breast cancer[52]. These mice exhibit an expansion of T cell-attracting, $CXCL9^+$ macrophages[52], a marker recently associated with better prognosis in several solid cancers[153]. Contrastingly, $TREM2^+$ macrophages often co-express secreted phosphoprotein 1 (SPP1), which is linked to cancer-promoting macrophages[153]. Importantly, TREM2-targeting antibodies synergize with PD-1 blockade to increase macrophage co-stimulatory capacities and consequently unleash T cell effector function in a subcutaneous mouse model of CRC[51]. TREM2 inhibition was also shown to increase IFNγ-induced immune activation, expansion of $CD8^+$ T cell numbers and better response to immunotherapy in glioblastoma[154]. However, TREM2 blockade is a challenging therapeutic strategy to implement, given the fine balance between its reported beneficial functions in curbing metabolic disorders[49,50] and its capacity to hinder anti-tumour response. Furthermore, the molecular mechanism underpinning the formation of $TREM2^+$ macrophages remains vague, since only a few metabolites – such as ceramide[155] and S1P[50] – were so far identified to directly induce *Trem2* expression. This is a key aspect to account for in the context of metabolic disorder-associated cancers given the altered levels of sphingolipids observed in patients with metabolic disorders[156], overall highlighting the key role of metabolism in the formation of this immunosuppressive macrophage subset. Notably, LAMs share similar features with $TREM2^+$ macrophages, including increased expression of immunosuppressive genes and enhanced lipid accumulation[80], justifying their inclusion under the LAM umbrella. However, it is plausible that not all LAMs are $TREM2^+$ macrophages, as exemplified by the fact that $PD\text{-}1^+$ TAMs recently identified in obesity were reported to be distinct from $TREM2^+$ LAMs[26]. Additionally, TREM2 can be cleaved and shed[50], and as such, it is not a consistent and reliable surface marker. Therefore, TREM2-focused studies must explore mechanisms underlying the emergence of LAMs and whether discrete populations with distinct cancer-modulating functions coexist in the LAM spectrum.

Macrophages can also contribute to metabolic dysregulation within the TME, with consequences on T cell functions. TAMs often express arginase-1 (*Arg1*), an enzyme that catabolizes arginine into urea and ornithine[157]. Activated T cells avidly uptake arginine to sustain their metabolic requirements, and arginine is crucial for the differentiation of anti-tumour memory T cells in tumour-bearing mice[158]. Therefore, macrophage-mediated arginine depletion may further reduce arginine levels in metabolic disorders, as seen in diet-induced, obese mice where the arginine-to-catabolite ratio is reportedly decreased[159]. This could in turn hinder T cell-mediated anti-tumour response in metabolic disorder-associated cancers. Macrophages can further catabolize ornithine into

polyamines[160], which are increased in obesity[161], and enforce T_H lineage commitment through epigenetic regulation[162] while impairing $CD8^+$ T cell function by suppressing T cell receptor (TCR) clustering[163]. Macrophages additionally express indoleamine 2,3-dioxygenase (*Ido1*), an enzyme that catalyses the conversion of tryptophan into kynurenine[43], a metabolite systemically increased in obese patients and HFD-fed mice[150]. Kynurenine has been shown to promote $CD8^+$ T cell PD-1 expression in cancer-bearing mice through the activation of aryl hydrocarbon receptors on T cells[164]. Given the capacity of macrophages to produce kynurenine[43], this may pose as another metabolite-mediated and macrophage-mediated immunosuppressive mechanism in metabolic disorder-associated cancers requiring further investigation. Itaconate, a metabolite upregulated in hepatic macrophages in patients with MASH and preclinical models of MASLD[165], induces $CD8^+$ T cell dysfunction in HCC by eliciting the expression of exhaustion markers through epigenetic regulation[166]. Hence, the role of macrophages in shaping T cell response in the context of metabolic disorder-associated cancers, as well as whether metabolic disorder-induced alterations in local and systemic metabolites impact this crosstalk, remains to be further explored. Therefore, therapeutically modulating macrophage recruitment and content may be useful in patients with metabolic disorders at high risk of developing cancer.

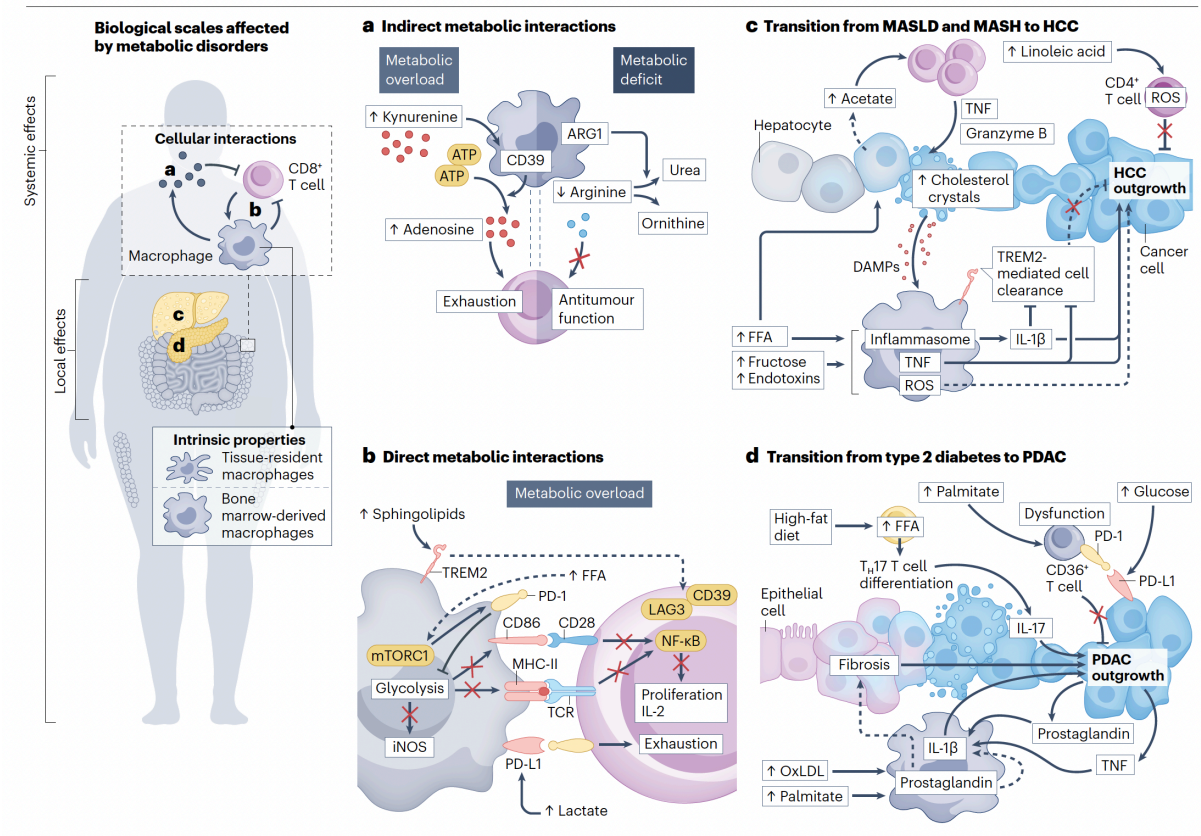

Fig. 2 | Metabolite imbalance alters immune cell phenotypes to promote oncogenic transformation. The metabolic imbalance in metabolic disorders influences the phenotype, crosstalk and functions of macrophages and T cells. The specific phenotype of these cells is influenced across biological scales. It is altered by intrinsic factors, cellular interactions, the local environment and systemic state. First, macrophages respond in an ontogeny-specific manner to the imbalance in metabolites and associated metabolic dysfunction. In turn, macrophage and T cell interactions are altered by indirect and direct mechanisms in the context of metabolic disorders, as shown in parts **a** and **b**. These cellular responses are context-dependent and affected by the organ in which macrophages and T cells reside, such as **part c** in response to metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH) in the liver, or **part d**

associated with type 2 diabetes (T2D) in the pancreas. In the context of metabolic dysfunction, a non-exhaustive list of systemic immune alterations include an increase in the numbers of monocytes, $CD8^+$ T cells and T helper 17 (T_H17) cells. **A**. Macrophages can hinder T cell effector activity through metabolic reshaping and competition. Similarly, metabolic disorder-associated metabolic alterations, resulting in the overload or deficit of metabolites, are linked to changes in macrophage phenotype, that alter T cell fate through macrophage–T cell crosstalk. Heightened levels of kynurenine, as seen in obesity, upregulate CD39 expression on macrophages, in turn through adenosine production, induce $CD8^+$ T cell exhausion. In parallel, macrophages expressing arginase-1 (ARG1) catabolize arginine into urea and ornithine. This limits arginine concentrations, hindering the anti-tumour function of T cells (as indicated by the 'x' mark). **B.** Macrophages can also inhibit T cell function through direct interactions. Expression of triggering receptor expressed on myeloid cells 2 (TREM2) on macrophages is initiated by metabolites, including the sphingolipids ceramides and sphingosine-1 phosphate (S1P). Although the bioactive mediators underlying this process remain largely unknown, as demonstrated by the dashed arrow, the sphingolipid ceramide induces $TREM2^+$ macrophages, which promote T cell exhaustion by stimulating expression of CD39 and lymphocyte activation gene 3 (LAG3). Obesity-associated metabolic alterations, such as circulating free fatty acids (FFAs), are hypothesized to promote macrophage programmed cell death protein (PD-1) expression in a mammalian target of rapamycin complex 1 (mTORC1)-dependent manner. In turn, PD-1 engagement in macrophages dampens glycolysis, which results in downregulation of CD86 and major histocompatibility complex (MHC II), inhibiting antigen-presenting capacity. This results in reduced cytotoxic activity as proliferation and interleukin-2 (IL-2) production are regulated through nuclear factor-κB (NF-κB)[293]. Furthermore, lactate can induce programmed death ligand 1 (PD-L1) expression on macrophages, which binds to PD-1 on T cells to promote exhaustion. **C.** Macrophages and T cells respond dynamically to the metabolic disorder-associated metabolite imbalance, often inducing an inflammatory state supporting the transition of MASLD to MASH to hepatocellular carcinoma (HCC). Hepatocytes exposed to FFAs are hypothesized to release increased levels of acetate, which increases tumour necrosis factor (TNF) and granzyme B release in auto-reactive T cells, promoting hepatocyte killing, triggering local inflammation and possibly increasing susceptibility to HCC development. Dying steatotic hepatocytes release cholesterol crystals and damage-associated molecular pattern (DAMPs) which induce macrophage inflammasome activation, and TNF and IL-1β release. In turn, TNF and IL-1β downregulate TREM2-mediated clearance of dying cells, which supports the progression to MASH. In addition, heightenend levels of fructose increases IL-1β secretion in macrophages by sensitizing them to endotoxins. Pro-inflammatory macrophages also contribute to ROS release, which aids in the transition to MASH and possibly HCC. Heightenend linoleic acid induces reactive oxygen species (ROS) generation, and the associated and selective cell death of $CD4^+$ T cells, allowing HCC progression. **D.** Similary, macrophages and T cells play important roles in the context of T2D to pancreatic ductal adenocarinoma (PDAC) transition. T_H17 cell abundance is increased in T2D patients. $CD4^+$ differentiation into T_H17 is induced in the context of high fat diet (HFD) through promotion of endogenous fatty acid production[294]. These cells can release IL-17 to promote chronic pancreatitis and PDAC malignant outgrowth. Palmitate induces $CD36^+$ T cell dysfunction, a process already occurring during pancreatic intraepithelial neoplasia (PanIN) lesions, indicating its involvement in cancer initiation. Heightened glucose levels increase PD-L1 expression in PDAC cells, thereby further limiting $CD8^+$ T cell mediated tumour killing[295]. Prostaglandin and TNF from PDAC cells induce IL-1β production in macrophages, fuelling cancer-promoting inflammation and suggesting that other sources of TNF and prostaglandin can contribute to this axis. Palmitate and oxidized low-density lipoprotein (oxLDL) can induce prostaglandin secretion from macrophages, an axis likely increased in the context of dyslipidemia in T2D.Prostaglandin, in turn, can contribute to pancreatic malignancy by promoting fibrosis. Small arrows indicate either upregulation (upward arrows) or downregulation (downward arrows). iNOS, inducible nitric oxide synthase; TCR, T cell receptor.

Metabolic-modulating therapies

Diet and exercise are lifestyle changes that can be beneficial in the management and treatment of metabolic disorders, as these behavioural changes are associated with weight loss and normalization of disease biomarkers (**Fig. 3A**). For instance, MASH and hyperglycaemia are improved following weight loss in patients with T2D[167]. However, patient adherence to these changes can be challenging, and long-term maintenance of dietary restrictions are often unsustainable, suggesting that pharmacological agents can also be valuable. In fact, given the large prevalence of metabolic disorders and their notable impact on patient health and quality of life, a plethora of disease-altering therapeutic strategies were developed in recent decades[168-171]. The mechanisms underlying this regulation are manifold and encompass immunomodulatory effects (**Fig. 3**), as explored in this section. The emerging consequences of the immune-altering effects of metabolic disorder-modulating therapies are discussed, including dietary approaches and pharmacological interventions, therefore, uncovering the potential of combinatorial approaches focused on macrophage remodelling and T cell-centric immunotherapy. Although beyond the scope of this Review, reports suggest that physical exercise also possesses immune-modulating properties that can shape carcinogenesis and therapy response[172]. Considering that exercise posits as a beneficial intervention in chronic diseases, including metabolic disorders[53,173], future work aimed at unraveling its potential as a treatment strategy in metabolic disorder-associated cancers is warranted.

Dietary approaches

Fasting diets

Fasting diets are dietary strategies involving temporary food deprivation[174]. Albeit caloric intake might be lowered in fasting diets owing to less frequent or content-controlled meals, recent studies suggest that their health effects extend beyond caloric deficit, ranging from autophagy-associated cellular repair, normalization of insulin secretion and sensitivity, reduced oxidative stress, weight loss, and adipocyte lipolysis and thermogenesis[174,175]. In light of these 'unintentional' consequences, fasting diets are currently under consideration as treatment strategies for different metabolic disorders, including obesity[174,176], MASLD, MASH[177] and T2D[178]. Fasting diets are also associated with immunomodulatory and cancer-regulating effects[179] (**Fig. 3A, B**), potentially influencing the outcome of metabolic disorder-associated cancers, as exemplified in a recent report, wherein intermittent fasting mitigated MASH features and hindered progression of MASH to HCC in animal models[180].

Fasting diets can modulate local and systemic myeloid-associated inflammation. For instance, in obese, HFD-fed mice restricted to a feeding window of 10h daily, decreased myelopoiesis through lower CCAAT/enhancer-binding protein α (*Cebpa*) expression was observed, consequentially hindering myeloid differentiation and limiting inflammation[181]. In mice fed a HFD regimen over 8 weeks, during which a 24 hour-fasting schedule was implemented three times per week, adipose tissue inflammation, macrophage infiltration and CLS numbers were reduced compared to mice fed a HFD freely[182]. Similarly, mice undergoing a regimen of 2-day HFD feeding and 1-day fasting exhibited heightened anti-inflammatory skewing of adipose macrophages through adipocyte secretion of vascular endothelial growth factor (VEGF)[183]. In mice subjected to a fasting regimen for up to 24 hours, increased levels of glucocorticoids promoted the activation of macrophage glucocorticoid receptor and consequently suppressed TNF secretion, leading to a glucocorticoid receptor-activated and

peroxisome proliferator-activated receptor alpha (PPARα)-dependent secretion of ketone bodies from hepatocytes[184]. Given the key role of TNF in driving MASH progression to HCC[93], this finding may support the use of fasting diets in this metabolic disorder-associated liver cancer by attenuating tumour-promoting TNF signalling.

Fasting diets can also regulate immune cell function in established cancers. In mice inoculated with CRC cells, alternate fasting days hindered immunosuppressive macrophage polarization and inhibited tumour growth[185]. *In vitro* mechanistic validation suggested that this effect was due to less tumour cell-derived adenosine secretion due to fasting induced downregulation of CD73 on cancer cells[185]. This can also be achieved with a fasting-mimicking diet, defined as a low-calorie, low-carbohydrate, low-protein regimen[186]. Indeed, in a study in which patients with breast cancer followed a 21 or 28 day regimen consisting of a 5-day fasting-mimicking diet (maximum of 600 calories on day 1, and 300 calories on days 2-5), followed by a refeeding period of 16 or 23 days, a reduction in the number of systemic immunosuppressive PD-L1$^+$ monocytes and CD15$^+$ granulocytes was reported, together with an increased abundance of cytolytic natural killer (NK) cells and intratumoural, activated CD8$^+$ T cells[186]. Fasting-mimicking diets can also hinder macrophage pro-tumorigenic function in mice with orthotopically injected breast cancer cells by decreasing glucose availability, slowing tumour growth[187]. Finally, combining a fasting-mimicking diet with immunotherapy elicited early exhausted effector T cells and reduced a tumour-promoting macrophage polarization, ultimately hindering tumour growth in mice orthotopically implanted with 4T1 breast cancer cells[188].

Overall, these findings suggest that fasting diets display immunomodulatory effects that could ultimately influence metabolic disorder pathologies and progression to the associated cancers. Exploiting fasting diet-induced macrophage polarization changes, combined with T cell-targeting immunotherapy, may hold therapeutic promise for patients presenting with metabolic disorder-associated cancers.

Ketogenic diet

Ketogenic diet is a high-fat, very low-carbohydrate, adequate-protein regimen that shifts the primary energy source of the body to ketone bodies[189]. In recent years, ketogenic diets have been explored as a therapeutic approach for T2D, obesity and cancer, given its reported beneficial role in reducing weight, hyperglycaemia, insulin resistance and systemic triglyceride levels[189]. These changes, together with the immunomodulatory effects of this diet[189], may impact tumorigenesis in metabolic disorder patients (**Fig. 3A, B**).

For instance, in healthy participants fed either a low-fat, vegan diet or a high-fat ketogenic diet, a systemic increase in activated CD8$^+$ and CD4$^+$ T cells was observed compared to the baseline measurements. The ketogenic diet specifically promoted CD16$^+$ NK cell abundance[190], cells that are beneficial for tumour control in cancer patients[191]. Interestingly, ketone bodies are preferred over glucose as an energy source for effector CD8$^+$ T cells[192]. In parallel, ketone bodies can also inhibit macrophage inflammasome formation[193] and sustain mitochondrial macrophage function to avert hepatic fibrosis development in MASLD-bearing, HFD-fed mice[194]. Notably, the ketogenic diet-associated ketone body increase also influences macrophage–T cell crosstalk by preventing PD-L1 expression in myeloid cells and inducing CXCR3$^+$ T cell expansion, ultimately boosting anti-PD1 response in tumour-bearing mice[195]. Overall, these findings highlight inflammation-dampening mechanisms that may potentially curb metabolic disorders and inflammation-associated cancers while improving cancer therapy response.

Interestingly however, following a ketogenic diet is associated with increased hepatic production and consequent increased plasma levels of growth differentiation factor 15 (GDF-15)[196], a molecule recently shown to be crucial for ketogenic diet-mediated reduction of energy intake and body weight in both mice and obese patients[196]. Despite this beneficial effect, GDF-15 is proposed as a biomarker of cancer and predicts poorer prognosis in many cancer types, including CRC and HCC[197]. GDF-15 displays immunomodulatory and cancer-regulating roles that may influence metabolic disorder-associated cancers. For instance, T2D patients with high GDF-15 plasma levels exhibit increased cancer incidence[198]. Similarly, high serum levels of GDF-15 are observed in patients with MASLD and MASH and predict disease severity[199]. Yet GDF-15 was shown to stimulate the expansion of anti-inflammatory macrophages and constrain fibrosis in a mouse model of liver fibrosis[200]. Anti-inflammatory macrophages also produce GDF-15 and consequently mitigate adipose tissue inflammation and systemic insulin resistance in HFD-fed and ob/ob mice[201]. Importantly, these findings were replicated using recombinant GDF-15 administration in these preclinical models of obesity, which led to enhancing macrophage oxidative function[201]. Although probably beneficial in metabolic disorders, the long-term consequences of promoting anti-inflammatory, immunosuppressive myeloid cell populations may fuel neoplastic outgrowth and cancer progression. Furthermore, GDF-15 was recently shown to hinder T cell-centric immunotherapy in cancer[202], suggesting caution for combinatorial approaches with a ketogenic diet.

Pharmacological modulation of metabolic disorders

Metformin

Metformin is the first-line agent and most commonly prescribed medication for T2D, acting chiefly by hindering liver gluconeogenesis[168]. The effects of metformin administration are manifold, encompassing inhibition of mitochondrial respiration, AMP-activated protein kinase (AMPK) activation, reduced caloric intake, and increased insulin sensitivity[168] (**Fig. 3C**). These wide-ranging changes have stirred interest in administering metformin in other metabolic disorders, including obesity, MASLD and MASH[203,204]. Mounting evidence also suggests that metformin can directly modulate the oncogenic process, suggesting a drug-repurposing potential for the treatment and prevention of cancers[168]. Indeed, metformin-treated T2D patients exhibit 31% reduction in overall cancer risk[205]. Organ-specific studies have shown a reduction in liver[206], pancreatic[206], breast[207] and colorectal[208] cancers in patients with T2D undergoing metformin treatment compared to other anti-diabetic agents. These beneficial effects in patients with metabolic disorders might be partially attributed to the reported immunomodulatory properties of metformin[168] (**Fig. 3C**).

Firstly, metformin treatment restricts the pro-tumorigenic role of macrophages through immune-metabolic rewiring. For instance, metformin impairs the production of pro-inflammatory cytokines by suppressing the fatty acid synthase-dependent palmitoylation of protein kinase B (PKB)[209] and reducing ROS in a zinc finger E-box binding homeobox 1 (ZEB1)-dependent manner[210]. In a study assessing acute inflammation in severe acute respiratory syndrome coronavirus 2 (SARS-CoV2)-infected patients, metformin was shown to hinder IL-1β and IL-6 secretion from macrophages in mice challenged with lipopolysaccharide (LPS), an endotoxin that elicits acute inflammatory response[211]. As these pro-inflammatory cytokines display established roles in promoting adipose inflammation and insulin resistance[34,150] as well as participating in the inflammatory background of cancers such as PDAC[103] and HCC[94], metformin effects, therefore, probably extend to metabolic disorder-associated cancers. In fact, in an HFD-fed zebrafish model of MASH-induced HCC, metformin limits the content of

TNF-producing macrophages, leading to reduced steatosis, DNA damage and hepatocyte proliferation[212]. These reports showcase myeloid-associated anti-inflammatory effects of metformin and suggest that its manifold anti-cancer properties might partially rely on limiting macrophage pro-tumorigenic functions.

Metformin can also regulate the immunomodulating properties and metabolic fitness of lymphocytes, with implications on their tumour-modulating capabilities. In aging-associated inflammation for instance, metformin promotes autophagy in T_H17 cells and consequently improves mitochondrial function *in vitro*[213] (**Fig. 3C**). The associated reduction in oxidative stress and in production of IL-17 reported in this study[213] could therefore curb the incidence of T2D-associated PDAC in patients treated with metformin, given the role of IL-17 in pancreatic carcinogenesis[144,145,147]. Moreover, by improving T cell mitochondrial function, metformin treatment rescued T cell motility in MASH-induced HCC mouse models, improving the efficacy of anti-PD1 and of the HCC standard-of-care combination of anti-PD-L1 and anti-VEGF treatments in this context[214]. Through promotion of AMPK activation, metformin was also shown to promote the anti-tumour activity of effector memory $CD8^+$ T cells in mice injected with distinct types of cancer cells[215]. Finally, metformin can boost PD-L1 degradation in the ER in cancer cells[216]. This effect consequently disrupts the immunosuppressive PD-1–PD-L1 axis on T cells, enhancing immunotherapy response when combined with anti-cytotoxic T-lymphocyte associated protein 4 (CTLA4) in distinct preclinical mouse models of cancer[216] (**Fig. 3C**). Whether metformin-induced PD-L1 degradation also occurs in macrophages remains to be established.

Given the apparent beneficial anti-cancer effect of metformin related to its immunomodulatory effects, there is potential to further improve patient outcomes by combining it with other immune-altering agents. For instance, metformin-mediated rewiring of macrophage function could be combined with agonists of CD40[217], a receptor highly expressed on antigen-presenting cells and a target for cancer therapy. In addition to re-polarizing macrophages towards a pro-inflammatory state[217], CD40 agonists were recently shown to elicit a macrophage-driven, T cell-independent anti-tumour response in melanoma-bearing mice by increasing FAO and glutamine metabolism[217]. Importantly, future studies on metformin use in metabolic disorder-associated cancers must also consider that, similarly to a ketogenic diet, metformin administration increases GDF-15 levels[218].

Statins

Statins are a widely-used class of drugs aimed at reducing cholesterol levels by inhibiting HMG-CoA reductase (HMGCR), a key enzyme involved in cholesterol production, thereby lowering the risk of cardiovascular disease in patients with hypercholesterolaemia[169] (**Fig. 3D**). Notably, the consequences of statin treatment extend beyond their cholesterol-lowering capacity, through, for instance, reshaping the microbiome composition[219] and modulating the immune system (**Fig. 3D**). Statins are also implicated in shaping tumorigenesis by directly inhibiting tumour growth or promoting apoptosis[220], and its use in patients is linked to reduced incidence for several cancer types, including CRC[221] and HCC[222]. Interestingly, despite the widely-reported side effects linking statins to increased T2D development[223], its use reduces the risk of PDAC in the general population[224] and in patients with T2D[225], and inhibits inflammation-associated PDAC development in mice[226]. Albeit the mechanism underlying the increased T2D risk in statin-treated patients is not fully understood[223], it highlights the

underappreciated complexity underlying the biological effect of statins, including their tumour-modulating properties.

Statins can modulate cholesterol metabolism on leukocytes and consequently shape their function and tumour-regulating capacities[83,227]. In preclinical mouse models of melanoma, cancer cell-induced activation of macrophage inducible Ca^{2+}-dependent lectin receptor (MINCLE) on TAMs promoted cholesterol synthesis, leading to ER stress and upregulation of immunosuppressive genes (such as *Arg1*) on these cells[83]. Statin-mediated blockade of macrophage cholesterol synthesis hindered this phenotype[83], suggesting that statins can also unleash anti-tumour activity. In T cells, cholesterol biosynthesis is crucial for IL-10 expression in human T_H1 cells, which is hindered upon statin treatment[228], suggesting that statins can be beneficial in countering an IL-10-mediated immunosuppressive TME. Interestingly, statins differentially modulate the intracellular cholesterol levels in T cells depending on their activation status; statins reduce cholesterol in naïve T cells, but increases its level in activated T cells, leading to reduced proliferative capacity[227]. In this study, T cell cholesterol accumulation was linked to impaired anti-tumour response[227]. These findings highlight that statins can regulate myeloid and lymphoid cells' cholesterol contents, exhibiting both beneficial and detrimental effects, however the net consequence of their use on immune control of tumour growth and development in patients with metabolic disorders remains to be fully established.

Statin treatment can also alter the expression of immune checkpoint molecule CD47 (also known as a 'do not eat me' signal). In a mouse model of atherosclerosis, statin treatment hindered CD47 expression on smooth muscle cells, augmenting macrophage-mediated efferocytosis and consequent clearance of atherosclerotic plaques[229]. As efferocytosis plays a key role in clearing debris and MASLD to MASH progression[50], this process might extend beyond atherosclerosis to benefit other metabolic disorders. Moreover, CD47 is commonly upregulated on cancer cells to prevent myeloid cell-mediated cancer clearance[230], suggesting that statin-associated CD47 hindrance could further boost anti-tumour immunosurveillance. Combinatory approaches using statins and drugs targeting the CD47–signal regulatory protein α (SIRPα) axis, which are currently being explored in the clinic[43], may be explored to boost macrophage-driven tumour control.

Emerging evidence also suggests that statins can modulate the microbiome as gut dysbiosis is less prevalent in patients with obesity who are treated with statins[231]. In mice, statin treatment also correlates with a reduction in microbiome-associated low-grade inflammation through secretion of indole-3-lactic acid. This microbiome-derived tryptophan catabolite blocks T_H17 differentiation and thus hinders IL-17-induced signalling, suppressing CRC tumourigenesis[219]. Given the reported role of IL-17-producing T cells in promoting PDAC development[144,146], including in the context of dysbiosis[147,148], this finding may further elucidate the anti-tumour functions of statins in metabolic disorder-associated cancers.

Together, these findings showcase the multifaceted consequences of statin treatment through reduction of cancer incidence, immune-metabolic modulation, and microbiome reshaping. Although most reports hint at a net beneficial effect in controlling metabolic disorders and tumour development, statins may also have a detrimental effect on activated anti-tumour T cells[227], highlighting the need to investigate a timely and/or tailored statin implementation in patients with metabolic disorders and cancer. Owing to the increased cholesterol metabolism in $TREM2^+$ TAMs[43], combining statins with TREM2-targeting strategies may prove fruitful and should therefore be explored in future studies.

GLP-1R agonists

Glucagon-like peptide 1 (GLP-1) is an incretin, a glucose-dependent, gut-derived hormone that elicits insulin secretion and lowers plasma glucose levels, while also supporting beta cell neogenesis and inhibiting their apoptosis[170] (**Fig. 3E**). Originally formulated for T2D patients, GLP-1 receptor (GLP-1R) agonists are incretin mimetics that display a longer half-life compared to endogenous GLP-1 (ref. 171). These drugs have seen a notable resurgence in recent years following the development of longer-acting formulations[171], such as semaglutide. Numerous studies now suggest their use is beneficial in other metabolic disorders by reducing caloric intake and promoting weight loss[232]. In patients that are overweight and non-diabetic, semaglutide also reduces cardiovascular disease-associated deaths[233]. Interestingly, GLP-1R agonist liraglutide mitigated pathological manifestations of MASH in humans by attenuating hepatic fibrosis progression and reducing steatosis[234]. Importantly, a recent study highlighted the reduced incidence of obesity-associated cancers, including CRC, PDAC and HCC, in patients with T2D treated with GLP-1R agonists[235], suggesting a role for GLP-1R agonists in shaping cancer susceptibility in metabolic disorders. As GLP-1R agonists attenuate local and systemic inflammation in humans and mice with obesity or T2D[232], their cancer-modulating effect may partly stem from their immunomodulating properties (**Fig. 3E**).

GLP-1R agonist administration can regulate local and systemic myeloid-associated inflammatory processes. In a mouse model of sepsis, GLP-1R agonist reduced systemic levels of myeloid-derived TNF induced by administration of TLR agonists[236]. Mechanistically, GLP-1R agonists elicited opioid-receptor and adrenergic-receptor signalling in the central nervous system, subsequently reducing peripheral inflammation[236], although the exact mechanism of this latter effect remains to be established. In ob/ob mice, GLP-1R agonists lowered adipose mass, inflammatory macrophage infiltration, and LPS-mediated inflammatory signalling through *Il6*, *Tnf* and *Ccl2* (ref. 237). In MCD-fed mouse models of MASH, liraglutide reduced fibrosis and the accumulation of pro-inflammatory macrophages, consequently reducing *Tnf* expression in the liver[238]. These immunomodulatory effects are potentially induced by the reduction of hepatic ceramide and sphingomyelin following GLP-1R agonist treatment[238], bioactive sphingolipids with well-known pro-inflammatory potential[156]. Liraglutide was also shown to promote anti-inflammatory macrophages in the livers of HFD-fed mice with MASH[239]. Overall, GLP-1R agonists might represent a preventative strategy for MASH-HCC patients, given that TNF is critical in driving MASH-induced HCC[93,118]. Their effect on dampening TLR signalling may also be beneficial given that patients with MASLD and MASH commonly present with gut dysbiosis, loss of intestinal barrier integrity and endotoxin translocation[240]. Moreover, as sphingolipids can bind to TREM2 receptors[155], whether the effect of GLP-1R agonists on hepatic sphingolipids alters $TREM2^+$ macrophage function, and consequently whether this can be combined with therapeutic approaches targeting $TREM2^+$ macrophages, will be an interesting research area to explore.

GLP-1R agonists can also regulate lymphocyte function. In diabetic-obese db/db mice, GLP-1R agonist administration reduced palmitate-induced T_H17 cell infiltration into pancreatic islets[241], which could potentially mitigate IL-17-associated PDAC development. GLP-1R agonists can also dampen TCR signalling on intestinal T cells to decrease the production of IFNγ and TNF, reducing local and systemic inflammation[242]. This report also suggests that GLP-1R agonist administration could hinder inflammation-associated CRC development[242]. Contrastingly, treatment with exendin-4 (a GLP-1R agonist) in T cells *in vitro* was shown to reduce the effector function and the survival of T cells expressing GLP-1R , while GLP-1R blockade promoted T cell infiltration and anti-tumour capacity in a CRC mouse model, suggesting that GLP-1R agonists may also hold tumour-promoting properties[243].

Beyond T cells, GLP-1R agonist was shown to improve NK cell metabolism, effector function and cytotoxicity without modulating NK cell content in patients with obesity, independently of weight loss[244]. This may hold important implications in obesity-associated cancers, given the known anti-tumoral role of NK cells[191]**.** With the broadening (and at times poorly justified) use of GLP-1R agonists, their impact on cancer requires further elucidation. More long-term data and mechanistic studies on this are thus warranted.

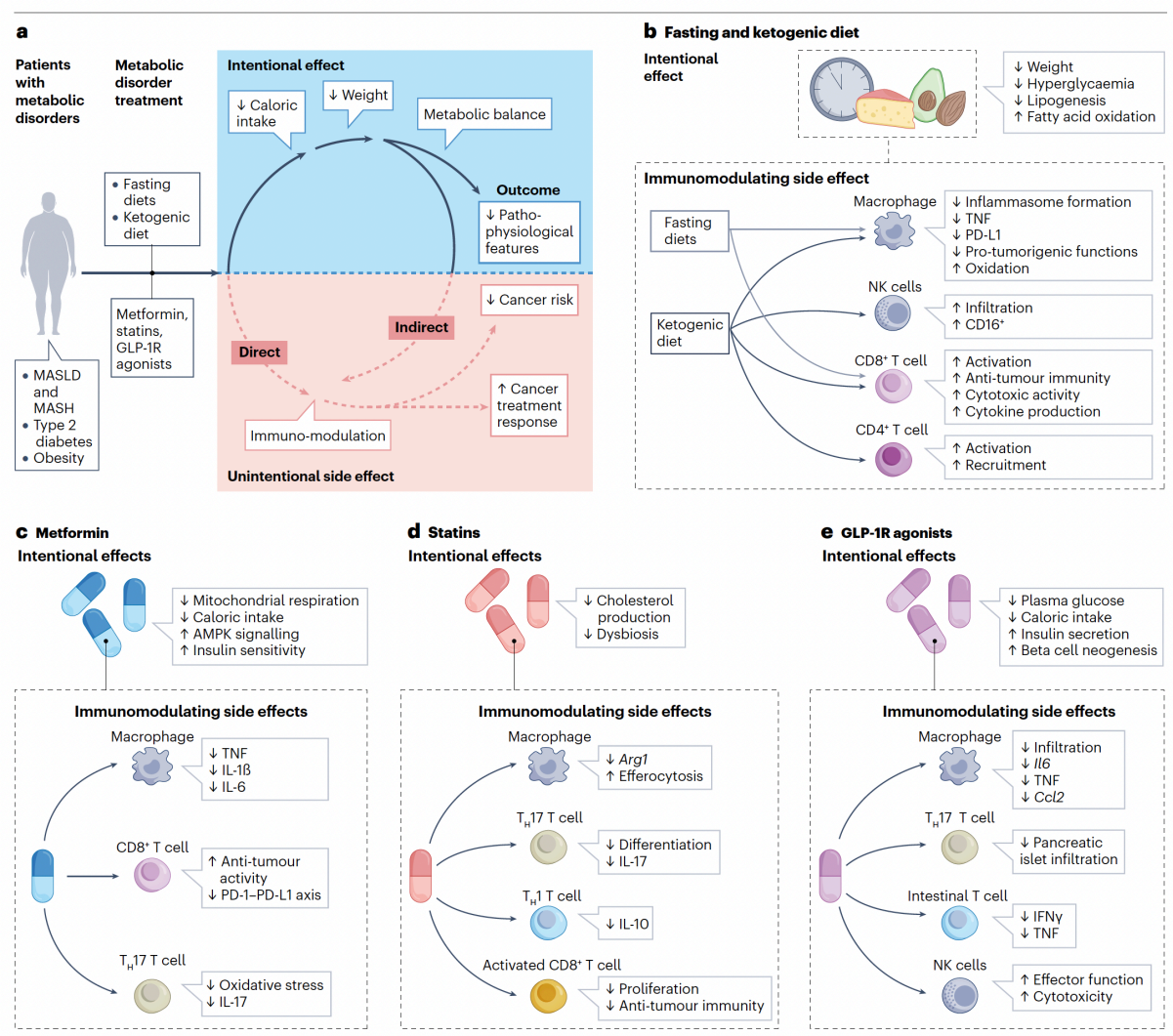

Fig. 3 | Metabolic disorder-targeting therapeutics interfere with cancer incidence and progression in an immuno-metabolic-dependent manner. A. Both dietary and therapeutic interventions are beneficial for treating metabolic disorders. They can lower caloric intake and patient weight, and restore metabolic balance and other pathophysiological characteristics of metabolic disorders. In parallel, these therapeutic interventions also possess unintentional, beneficial side effects that alter immune phenotypes, which could reduce cancer risk or improve therapy response in patients with cancer. A dashed line is used here to indicate that these relationships are currently under investigation. **B**. Although they can be challenging to adhere to, metabolic disorder-intervening diets, for example, through fasting diets or ketogenic diets, result in weight loss, decreased hyperglycaemia and decreased lipogenesis, while increasing fatty acid oxidation. Unintentionally, these diets and their associated metabolic alterations impact the immune system and, therefore, tumourigenesis by decreasing macrophage pro-inflammatory programs and increasing T cell and natural killer (NK) cell-mediated anti-tumour potential. **C**. Metformin is widely used as medication for type 2 diabetes (T2D) owing to its ability to increase insulin sensitivity, while also decreasing caloric intake, activating AMP-activated protein kinase (AMPK), and

hindering mitochondrial respiration. In addition, metformin possesses immune-modulatory functions, including decreasing pro-inflammatory skewing of myeloid cells (including macrophages), lowering oxidative stress and interleukin 17 (IL-17) production by T helper 17 (T_H17) cells and increasing anti-tumour capacity of $CD8^+$ T cells. **D.** Statins are widely used to inhibit cholesterol biosynthesis in patients with hypercholesterolaemia, lowering the risk of cardiovascular disease. While statins lower the incidence of cancer, the mechanisms driving its anti-tumoral effect are still under investigation. Nevertheless, statins display immune-modulatory features, altering the pro-tumorigenic phenotype of macrophages, T_H17 cells, differentiation and inflammatory capacity of T_H1 cells and proliferation of activated $CD8^+$ T cells. **E.** Glucagon-like peptide 1 receptor (GLP-1R) agonists are pharmacological agents originally devised for T2D and are now used to reduce obesity and potentially treat other metabolic disorders (including metabolic dysfunction-associated steatohepatitis (MASH)). GLP-1R agonists alter the pro-inflammatory phenotypes of macrophages, intestinal T cells, T_H17 cells, and NK cells. Small arrows indicate either upregulation (upward arrows) or downregulation (downward arrows). *Ccl2*, C-C motif chemokine ligand 2; MASLD, metabolic dysfunction-associated steatotic liver disease; IFNγ, interferon-γ; IL-1β, interleukin 1-β; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; TNF, tumour necrosis factor.

Conclusions and perspectives

The complex mechanisms underpinning the frequent occurrence of cancers in patients with metabolic disorders unequivocally showcases the role of metabolism and immunity in shaping the tumorigenic process. Indeed, although cancer-intrinsic metabolic rewiring and metabolic competition in the cancer milieu have been extensively studied in recent years[29-31], much remains to be unraveled, particularly in metabolic disorders. In tandem, evidence suggests a critical role of immune cells in driving metabolic disorder initiation and maintenance[34], while also shaping oncogenic transformation, progression and therapy response in metabolic-associated cancers[25,26,91,93,118,138]; this overall highlights the dichotomic role of immunity not only in supporting homeostasis but also driving disease development.

Naturally, immune-targeting and metabolic-targeting pathways are touted as promising therapeutic interventions for distinct cancer types[31,245]. The design of future clinical studies harnessing these axes requires careful consideration of the altered metabolic and immune landscape in patients with metabolic disorders. Similarly, with cases of cancer and metabolic disorders rising[4,28,246] and the increasing number of patients prescribed with metabolic disorder-altering drugs, particularly GLP-1R agonists, whose prescription rates have increased substantially for non-diabetic patients in the USA in recent years[247] , further investigations are warranted to dissect how these therapies alter the immune system, and both local and systemic metabolic processes.

The rise in availability, affordability and capabilities of -omics technologies at single-cell resolution is revolutionizing how the complex interactions within the TME can be investigated in many cancer types. By integrating spatial and temporal information of metabolic and immune factors from relevant preclinical and patient materials, the particularities underlying the connection between metabolic disorders and cancer ought to be further deciphered. In this context, investigating how metabolic dysfunction shapes immunity and how they collectively drive pathological features of metabolic disorder-associated cancers may hold implications for the whole cancer field, by potentially exposing novel therapeutic vulnerabilities targeted at cancer immune-metabolic pathways. Similarly, advances in this area may also impact our understanding of the implications of comorbid metabolic disorders in cancers whose incidence is not necessarily linked to underlying metabolic dysfunction, such as lung or skin cancers[22].

Ultimately, addressing the dual burden of metabolic disorders and metabolic disorder-associated cancers is of paramount importance for public health in the coming decades. Fostering interdisciplinary research efforts is essential to mitigate the growing impact of these interconnected epidemics and apply novel knowledge to a larger breadth of patients suffering from systemic metabolic syndromes and cancers beyond those discussed in this Review.

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Competing interests

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Table of Content Summary

Metabolic disorders, such as obesity, metabolic dysfunction-associated steatotic liver disease (MASLD), metabolic dysfunction-associated steatohepatitis (MASH), and type 2 diabetes, are increasingly recognized as significant contributors to cancer development. Here, Taranto, Kloosterman and Akkari explore their influence on tumour progression through the metabolic interactions of macrophages and T cells to alter immune function and cancer outcomes.

Author contributions

L. A. and D.T. researched data and wrote the article. All authors contributed substantially to the discussion of the content and reviewed and/or edited the manuscript before submission.

Glossary

Adaptive immunity

White blood cells, including T cells and B cells, that can recognize specific antigens and form long-lasting memory cells to protect the host against pathogens.

Adenosine

A nucleoside molecule that serves as a building block in RNA and DNA and that is also involved in other cellular processes, including immunomodulation and metabolism.

Adipocyte hypertrophy

Enlargement of adipocytes associated with augmented fat storage that is a common feature in the pathogenesis of metabolic disorders.

Antigen-presenting cells

Specialized immune cells that uptake, process and display antigens on their surface to activate other immune cells.

Beta cells

Insulin-producing cells in the pancreas that reside within clusters known as pancreatic islets.

Damage-associated molecular pattern (DAMP)

Molecules that are released by stressed, injured or dying cells that can trigger an inflammatory response in immune cells upon their recognition via specialized receptors.

Dysbiosis

Imbalance in the microbiota composition of an individual that is associated with adverse health effects.

Dyslipidaemia

Abnormal levels of any or all lipids in the bloodstream.

Efferocytosis

Process by which professional phagocytic cells remove dying cells, thus preventing overt inflammation and collateral damage.

Ferroptosis

An iron-dependent form of cell death driven by overt oxidative stress.

Hepatic steatosis

Abnormal accumulation of fat within hepatocytes in the liver.

Hypercholesterolaemia

Abnormally high levels of cholesterol in the bloodstream.

Hyperglycaemia

Abnormally elevated levels of glucose in the bloodstream.

Inflammasome

Molecular machinery formed in response to danger signals and that is involved in the processing and activation of inflammatory mediators.

Innate immune cells

White blood cells, including macrophages and neutrophils, that serve as the host's first line of defence against pathogens and other foreign entities without the need for prior contact or specific recognition.

Insulin

Hormone secreted by pancreatic beta cells to control blood glucose levels.

Ketone bodies

Water-soluble molecules produced by the liver in glucose-restricted and fasting conditions as a source of energy.

Lipid-associated macrophages

Macrophages with increased lipid accumulation that play a key role in inflammation and lipid metabolism, and are observed in many pathologies, such as atherosclerosis, MASLD, and obesity.

Lipid peroxidation

A chain reaction where oxidative degradation of lipids occurs as a result of reactive oxygen species reaction with polyunsaturated fatty acids in the cellular membrane.

Lipotoxicity

Harmful effect of lipid accumulation in non-adipose tissue, which can lead to cellular dysfunction, oxidative stress, ER stress, and cell death.

Methionine-deficient and choline-deficient diet

A dietary preclinical model of MASH lacking the nutrients methionine and choline, leading to progressive accumulation of hepatic lipid and fibrosis without cancer development.

Myelopoiesis

The process where myeloid cells, including granulocytes, dendritic cells and monocytes, are produced by hematopoietic stem cells within the bone marrow.

Pancreatic intraepithelial neoplasia

Small precancerous lesions in the pancreatic duct that may progress to pancreatic adenocarcinoma.

Reactive oxygen species (ROS)

Highly reactive molecules derived from oxygen, including hydrogen peroxide and superoxide radical, that can cause cellular damage.

Sphingolipids

A class of lipids derived from the amino alcohol sphingosine, involved in cell signalling, inflammation, cell growth and differentiation.

Tables

Table 1: Beyond macrophages and CD8$^+$ T cells: metabolic disorder-associated alterations of other immune cells and their influence on tumorigenesis

Cell type	Alterations in metabolic disorders	Metabolite impact on immune cell function	Metabolic disorder-promoting features	Cancer-promoting features in metabolic disorder-associated tumorigenesis
Dendritic cells	Decreased dendritic cell migration to lymph nodes in obese mice[248] Decreased dendritic cell antigen presentation due to increased oxidative stress in HFD-fed mouse models[249] Increased cDC1 abundance and activation in humans and mice with MASH[117]	Extracellular triglycerides impair dendritic cell antigen processing and presentation in tumour-bearing mice and human cancer patients[250] Lactate hinders dendritic cell maturation, activation and antigen presentation in mice and human dendritic cells *ex vivo*[251]	cDC1s drive obesity-associated inflammation in mice through IL-12 secretion and promotion of macrophage accumulation[252] XCR1$^+$ cDC1s promote T cell-driven inflammation to foster MASH in a mouse model[253]	XCR1$^+$ IDO$^+$ cDC1s correlate with a high-risk signature for MASLD to HCC progression in patients with MASLD[254]
Mucosal-associated invariant T (MAIT) cells	Decreased MAIT cells in the blood, ileum and epididymal adipose tissue of obese HFD-fed and ob/ob mice, and systemically in patients with obesity and T2D[255]	Hyperglycaemia may induce MAIT cell apoptosis in mice[255]	MAIT cells induce dysbiosis, insulin resistance, and show a pro-inflammatory phenotype by producing more IL-17 in the ileum and TNF and IL-17 in adipose tissue of obese mice[255]	MAIT cells were recently shown to be dysfunctional in HCC in human and mice through a PD-1/PD-L1 interaction with TAMs[256]. Whether this occurs in MASH-induced HCC or in other metabolic disorder-associated cancers remain to be established*
Natural killer (NK) cells	Increased NK cell number in visceral adipose tissue of obese mice[257] Decreased systemic numbers of NK cells in humans and mice with obesity[258], patients with T2D[259] and patients with MASLD[260] Increased CD56^{bright} and decreased CD56^{low} NK cell numbers in liver of patients with MASLD[260] Decreased NK cell effector function in T2D in patients[259] and degranulation capacity in humans and mice with obesity[258]	Lactate suppresses NK cell function in human melanoma[261] FFAs hinders NK cell activation and cytotoxicity in humans and mice with obesity[258]	NK cell-derived IFNγ mediates macrophage infiltration, inflammation and insulin resistance in HFD-fed mice[257] NK cells promote hepatic fibrosis in human MASLD[260] NK cells foster resolution of hepatic fibrosis in a MASH mouse model[262]	The role of NK cells in metabolic disorder-associated cancers remains underexplored and requires further investigation*

Natural killer T (NKT) cells	Increased NKT cell numbers in mouse and human liver MASH[263]** Decreased function cytotoxicity and increased lipid peroxidation in hepatic NKT cells in mice with MASLD-induced HCC[264]	Cholesterol drives NKT cell dysfunction in hepatic NKT cells of mice with MASLD-induced HCC[264] Secondary bile acids inhibit hepatic CXCR6$^+$ NKT cell infiltration in primary and liver metastases mouse[265]***	NKT cell-derived TNFSF14 promotes MASH development through increased hepatocyte lipid uptake and hepatic stellate cell activation[263]	NKT cell derived TNFSF14 activates NF-κB on hepatocytes to fuel MASH progression to HCC in mice[263] NKT cell dysfunction allows MASLD-induced HCC development in high-fat, high-carbohydrate diet-fed mice[264]
Neutrophils	Increased systemic neutrophil numbers in patients with morbid obesity[266,‡] Increased neutrophil abundance in the liver of humans and mice with MASH[33] Increased neutrophil abundance in adipose tissue of HFD-fed mice[267] Increased systemic neutrophil-to-lymphocyte ratio in T2D patients[268] Increased neutrophil NETosis in T2D[269] and MASH[270] mice models	Elevated ROS in human neutrophils in vitro[271], high glucose in the serum of patients with diabetes[272] and increased FFAs in mouse neutrophils *in vitro*[270] are associated with neutrophil NETosis	Neutrophil NETosis promotes macrophage activation and inflammation in a mouse model of MASH[273] Neutrophil NETosis impairs wound healing and fosters inflammation in mice with diabetes[269] Neutrophil NETosis induces vascular dysfunction in obese mice[274]	PD-L1$^+$ neutrophils contribute to progression of PanIN lesions to PDAC via IL-1β and NETosis in HFD-fed KC mice[275] Neutrophils fuel obesity-associated desmoplasia and PDAC growth in HFD-fed mice[276] Neutrophil NETosis is associated with macrophage infiltration, inflammation and HCC development in a mouse model of MASH[270] CXCR2$^+$ neutrophils limit T cell-centric immunotherapy response in a mouse model of MASH-induced HCC[277]
Regulatory T (T_{reg}) cells	Abundance is decreased in subcutaneous and visceral adipose tissues in patients with obesity, and in visceral adipose tissue of long-term HFD-fed mice[278,279]	Unlike effector and cytotoxic T cells, T_{reg} cell function and proliferation are not affected in a high-lactate, low-glucose tissue environment in mice[280] Lactic acid induces PD-1 expression on T_{reg} cells in highly glycolytic tumours in humans and mice[281] BCAAs promote T_{reg} cell proliferation and immunosuppressive function in mice[282] Lipid uptake is increased in intratumoural T_{regs} through CD36 upregulation in mice and humans with cancer and is critical for T_{reg} survival in the lactic acid-enriched TME[283]	Loss of T_{reg} cells contributes to adipose tissue inflammation and insulin resistance patients living with obesity[279]	NETosis-driven T_{reg} cell expansion suppresses CD8$^+$ T cell immunosurveillance in mouse models of MASH-induced HCC[284]

The references herein cited depict recent and relevant immune-associated changes offering a link between metabolite alterations and metabolic-associated cancers and is not an exhaustive list. ‡Morbid obesity is defined as body mass index (BMI) ≥40 kg/m² [5]. * To the best of our knowledge. ** This study identified NKT cells as $CD57^+$ $CD3^+$ cells, a set of markers that cannot fully exclude mucosal-associated invariant T cells, a rare subset of T cells that are nevertheless significantly more abundant in human livers compared to murine livers in homeostatic conditions [256]. *** This study suggests that MAITs also express C-X-C chemokine receptor 6 (CXCR6) and thus may also be involved in this process. BCAA, branched chain amino acid; cDC1, type 1 conventional dendritic cell; FFA, free fatty acid; HCC, hepatocellular carcinoma; HFD, high-fat diet; IDO1, indoleamine 2,3-dioxygenase; IFN-γ, interferon gamma; IL-12; interleukin-12; KC, $Kras^{G12D}$, Pdx1-Cre mice, a mouse model for pancreatic cancer. MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis; MHC, major histocompatibility complex; NET, neutrophil extracellular trap; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B-cells; PanIN, pancreatic intraepithelial neoplasia; PD-1, programmed cell death protein 1; PDAC, pancreatic adenocarcinoma; PD-L1, programmed death-ligand 1; ROS, reactive oxygen species; T2D, type 2 diabetes; TAM, tumour-associated macrophage; TNF, tumour necrosis factor; TNFSF14, tumour necrosis factor superfamily members 14; T_{reg}, regulatory T cells; XCR1, X-C motif chemokine receptor 1

Boxes

Box 1 | Metabolic disorders: paving the way to cancer

Global incidence of metabolic disorders

Obesity is a chronic disorder characterized by excessive fat accumulation that eventually impacts patient health and increases the risk for comorbidities, such as cardiovascular diseases and cancer[5]. Obesity has reached epidemic levels in recent years, affecting an estimated 504 million women and 374 million men in 2022 worldwide[1]. Pathophysiological features underlying obesity development are multifactorial and extend beyond sedentary lifestyle and surplus in caloric intake to also include genetic predisposition[5] (**Fig. 1A**). Body mass index (BMI) has been extensively used to define and measure obesity, despite obvious shortcomings, as BMI does not distinguish lean mass from fat mass and fails to identify patients who are metabolically healthy and at a lower risk of developing metabolic syndrome[296]. Conversely, metabolically unhealthy patients with obesity exhibit metabolic dysfunction-associated conditions, including high glucose levels (hyperglycaemia), reduced sensitivity to insulin, and higher visceral fat accumulation[296].

From 2016 onwards, the prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) is estimated as ±37.8% of the global population[3]. Its defining feature is excessive hepatic fat buildup in hepatocytes or steatosis (increased fat deposition in the liver). This lipid accumulation is a consequence of lipid metabolism alteration, caused by increased uptake of exogenous sources of lipids and/or accumulation of lipids derived from *de novo* lipogenesis[6,297]. The progressive lipid buildup in MASLD is a required step for the development of metabolic dysfunction-associated steatohepatitis (MASH), a more advanced disease during which liver injury, hepatocyte death and inflammation often occur in tandem with hepatic fibrosis[6]. Albeit often co-occurring with obesity, MASH can also be present in lean individuals (such as MASH linked to *PNPLA3* polymorphism), who exhibit increased visceral adiposity[298].

Type 2 diabetes is the most common form of diabetes; it is a chronic metabolic disorder characterized by the body's inability to control glucose levels and is associated with uncontrolled hyperglycaemia and hyperinsulinemia[7]. Reduced insulin sensitivity often precedes the development of T2D[7]. These conditions eventually foster full-blown T2D, wherein pancreatic beta-cells are unable to secrete enough insulin to compensate for insulin resistance and can eventually undergo apoptosis[7]. T2D is estimated to affect ±6.1% of people worldwide (where high body mass index (BMI) accounts for ±52.2% of T2D cases), and is expected to afflict more than 10% of the population of close to half of the world's countries by 2050 (ref. 2). T2D development is closely tied to sedentary lifestyles, increased body weight and obesity, overnutrition, pancreatic fat accumulation and also genetic predisposition[7,8] (**Fig. 1A**).

These three metabolic disorders are often interconnected (**Fig. 1A**). MASLD and T2D often co-occur and share similar pathologies, including hepatic insulin resistance and liver inflammation[299]. Patients with MASLD are twice as probable to develop T2D as patients without MASLD, irrespective of obesity, and T2D risk correlates with the degree of hepatic fibrosis and cirrhosis[299]. T2D itself is linked to hepatic fibrosis in patients with obesity and MASLD and is a risk factor for MASLD-to-MASH progression in humans[299,300].

Cancer susceptibility in metabolic disorders

Apart from the health burden inherent to metabolic disorders, many cancer types — particularly of the gastrointestinal tract — are more common in these patients (**Fig. 1A**)[22]. Excess body weight (defined as individuals above the non-obese weight range of 18.5 to 24.9 BMI) is associated with increased risk for the development of several gastrointestinal cancers. By comparing individuals with a BMI below 40, with those with a BMI of 40 or more, the relative risk (95% confidence interval) for cancer development is increased to 4.8 (3.0-7.7) for oesophageal adenocarcinoma, 1.8 (1.3-2.5) for stomach cancer, 1.3 (1.3-1.4) for colorectal cancer (CRC), 1.8 (1.6-2.1) for liver cancer, 1.5 (1.2-1.8) for pancreatic cancer, and 1.3 (1.2-1.4) for gallbladder cancer[22]. Obesity is also closely tied to the development of postmenopausal breast cancer (1.1 relative risk; 1.1-1.2)[22].

In patients with MASLD and MASH, ongoing liver damage and chronic inflammation can lead to the development of hepatocellular carcinoma (HCC), with an annual HCC incidence of 2.4-12.8%[6]. In fact, MASH is currently one of the most common risk factors associated with HCC, and the number of patients with MASH-induced HCC are expected to increase in the coming years owing to shifts in global diet patterns[301].

T2D patients exhibit a hazard ratio for cancer-related death of 1.25 (95% confidence interval, 1.19-1.31) compared to the general population[302] and are at higher risk for many cancer types, including CRC (relative risk 1.36; 1.23-1.50), liver (relative risk 2.50; 1.8-3.5) and pancreas (relative risk 1.94; 1.53-2.46)[23]. Orthogonally, PDAC patients are at a greater risk of developing new-onset T2D[303].

Box 2 | Macrophages bridge metabolic disorders and liver metastasis

The liver is a common site for metastatic outgrowth of many primary cancers, including breast cancer, pancreatic ductal adenocarcinoma (PDAC) and colorectal cancer (CRC)[304]. The tumour microenvironment (TME) of metastatic sites is often immunosuppressive. This is also evident for liver metastases, including those from primary PDACs and CRCs, which are both reported to be tumour-permissive and macrophage-enriched[305,306]. Metabolic disorder-driven nutrient and metabolic rewiring, and consequent immunomodulation may collectively fuel metabolic disorder-associated hepatic metastasis. Both metabolic dysfunction-associated steatotic liver disease (MASLD)[39] and type 2 diabetes (T2D)[40] are associated with increased CRC metastasis to the liver, and obesity. The associated increase in hepatic lipids can promote both melanoma- and breast cancer liver metastasis[41]. Emerging macrophage-associated mechanisms that may provide a connection between metabolic disorders and facilitate liver metastasis outgrowth are outlined below.

In mice with high-fat diet (HFD)-induced MASLD, hepatic metastasis was shown to depend on macrophage upregulation of NOD-like receptor C4 (NLRC4), a component of the inflammasome machinery[307]. In turn, NLRC4-, palmitate-induced and interleukin 1β (IL-1β) secretion on tumour cells promoted $CD206^+$ immunosuppressive macrophage accumulation and CRC outgrowth[307].

Secreted phosphoprotein 1 $(SPP1)^+$ macrophages are present in patients and mice with MASLD, wherein they limit hepatic steatosis by promoting fatty acid oxidation[308]. However, $SPP1^+$ macrophages were shown to accumulate and possibly drive CRC liver metastasis in patients[309], suggesting that the promotion of $SPP1^+$ macrophages in MASLD could enhance metastatic seeding in the MASLD-afflicted liver. Similarly, $TREM2^+$ macrophages, which are abundant in the liver of patients

with metabolic dysfunction-associated steatohepatitis (MASH)[18], were shown to shield cancer cells from anti-tumour immunosurveillance to foster breast cancer lung metastasis[310]. This suggests that a similar mechanism may occur in MASH-associated hepatic metastases. Moreover, obesity can skew myeloid lineage development to support breast cancer liver metastasis by inducing Ly6C^{high} monocytes[311]. Depletion of this subset through C-C chemokine receptor type 2 (CCR2) inhibition reduced the presence of exhausted CD4^{+} T cells, suggesting an immunosuppressive role for these myeloid cells. Alluding to the tumour-promoting role of CCR2^{+} myeloid cells, CRC liver metastasis is reduced in the context of CCR2 and C-C motif chemokine 2 (CCL2) blockade in mice[312].

CD36^{+} macrophages can also support liver metastasis. CD36-mediated uptake of extracellular vesicles (EVs) containing tumour-associated long-chain lipids, rewires macrophage metabolic programme, consequently supporting an immunosuppressive phenotype[313]. Blocking this population hindered hepatic metastasis in mice injected with different cancer cell lines[313], suggesting that CD36^{+} macrophages, which occur in metabolic disorders[49], may also have a role in liver metastasis in patients with metabolic disorders.

Lastly, steatotic hepatocytes in HFD-fed, MASLD-bearing mice secrete microRNA-loaded EVs, and these structures also increased in the serum of patients with MASLD[314]. MicroRNA-containing EVs, in turn, promoted the activation of the oncogene Yes-associated protein (YAP) on CRC cells inoculated in these mice, leading to the infiltration of immunosuppressive macrophages that hindered CD8^{+} T cell function, overall promoting CRC liver metastasis in the context of MASLD[314].

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