Metabolism and lipid mediators as regulators of innate immune cell function: implications for inflammation and immune responses

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VI

General Discussion

Introduction

In this thesis we have touched upon the topics of both cell intrinsic and paracrine effects of lipid metabolism (Fig. 1). In **chapters 3** and **4** we described how IgG and IgA induce distinct metabolic reprogramming via Fc receptors, with IgG needing FA synthesis, and IgA requiring mitochondrial respiration and COX2 activity to boost macrophage inflammatory responses. Finally, in **chapter 5** we reported how pathogen-derived glycans, following binding to Dectin-1 and -2, instruct DCs to oxidize lipids via COX 2, resulting in the synthesis of PGE_2 followed by autocrine signalling, licensing DCs for Th2 priming.

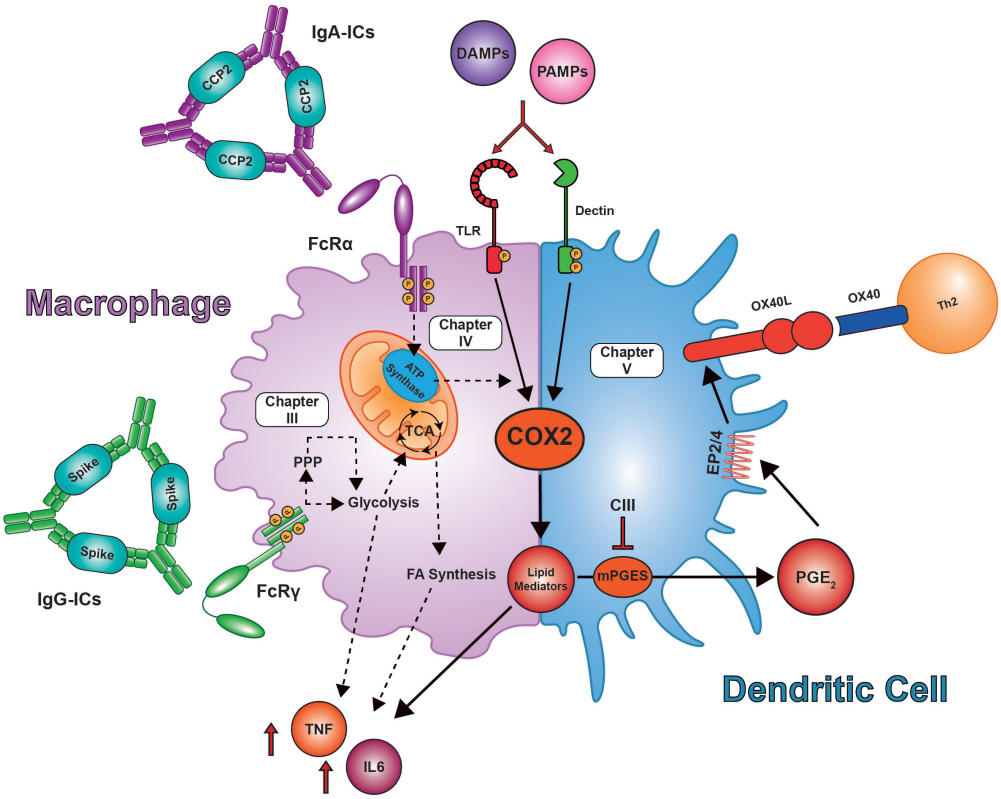

Figure 1: Macrophage and Dendritic Cell functions are regulated by metabolism and lipid mediators. Anti-Spike IgG-ICs reprogramme macrophage metabolism via Glycolyis, PPP and FA synthesis to induce a hyper-inflammatory state. Similarly, anti-CCP2 IgA-ICs boost the inflammatory potential of macrophages via ATP synthase and COX2, resulting in increased synthesis of lipid mediators, TNF and IL6. In DCs, antigens from *S. mansoni* eggs bind to Dectin and induce OX40L expression and subsequent Th2 priming in a PGE_2-dependent manner, which can be chemically targeted with CIII, a specific inhibitor of mPGES.

Lipid Metabolism Within Myeloid Cells

The work presented in this thesis point to a central and vital role of intrinsic lipid metabolism in driving myeloid cell immune responses, and showcases its plasticity, resulting in drastically different immune cell phenotypes, depending on the stage of cellular differentiation and which stimulus the cell encounters.

We have seen that antibodies induce a different metabolic reprograming in macrophages via FcR engagement, depending on both their isotype and subclass. IgG seems to rely on glycolysis, PPP and FA synthesis to induce an inflammatory phenotype in macrophages. However, we found that IgA, contrary to what we observed for IgG in macrophages, and contrary to what was seen for IgA in DCs (1), does not require glycolysis to increase the inflammatory potential of macrophages. Interestingly, not only that, but we observed that within the two IgA subclasses, i.e. IgA1 and IgA2, different metabolic requirements exist for cell activation. While IgA1 does not seem to rely on any specific metabolic pathway, IgA2 seems to be dependent on mitochondrial metabolism, more specifically, ATP Synthase activity, to induce a hyper-inflammatory phenotype in macrophages. Together, these studies point towards a complex relationship between pathologies, cellular metabolism and immune function.

Key factors that are likely to underpin these differences in metabolic reprogramming and dependencies are tissue microenvironment, cell type and nature of Fc receptor signalling. For example, while generally macrophages rely on glycolytic metabolism to mount a pro-inflammatory response in response to pathogens (2) this is not always the case and can be dictated by the tissue microenvironment they reside in (3). Alveolar macrophages, as opposed macrophages in other tissues, are well known for relying on OXPHOS instead of glycolysis for their inflammatory response (4), due to being adapted to an oxygen-rich environment. In the case of RA, during inflammation, the synovium undergoes repeated cycles of hypoxia and re-oxygenation (5–8). These hypoxia conditions have been shown to induce COX2 expression (9), and the repeated oscillations of oxygen availability was reported to induce the production of ROS with a HIF1a-stabilizing effect (10–12). The expression of COX2, and hypoxia-driven ROS and subsequent HIF1α activation were shown to drive inflammation in both macrophages and neutrophils (9,13,14). Therefore, one could hypothesise that this IgA2-ATP Synthase-COX2 axis in macrophages is part of a broader RA-specific physiological mechanism of inflammatory potentiation to induce mitochondrial ROS, HIF1α stabilization and subsequent proinflammatory cytokine synthesis (15,16).

As for the case of Fc receptor signalling, it is known that, in humans, only certain cell types express FcαRI (e.g. monocytes, macrophages or DCs) (17). Even within

those populations, the expression of FcαRI is variable, e.g. while it is expressed by most macrophage populations, it is not expressed by intestinal macrophages, while for DCs its expression is mainly restricted to interstitial DCs, monocyte-derived DCs and CD34+-derived DCs (17–19). This showcases that, depending on the tissue localization of the cell, they may reduce, or even lose, the expression of IgA-binding receptors. This can lead us to hypothesize that, if an immune cell population expresses IgA-binding receptors to different degrees depending on their tissue niche, they might also have a different metabolic response to IgA, depending on the function of the cell, and the tissue where it resides. Additionally, it has been described that different Fc receptors have different signalling pathways (20), so it is conceivable that FcαRI stimulation might induce a different metabolic reprogramming than FcγR stimulation. Secondly, it was already shown, for IgG, that different isotypes induce different signalling pathways, different metabolic reprogramming, and subsequently differences in cytokine production (21). Our work suggests a similar phenomenon applies to IgA1 and IgA2. This, however, raises more questions – Is this due to differences in binding strength/affinity between IgA subclasses and/or different glycosylation profiles and the FcαR, analogous to what has already been described for IgG (22,23)? Hypothetically, could there also be an IgA2-specific receptor/signal transducer that induces certain complementary activation states or, on the other hand, is there an IgA1-specific receptor/signal transducer that inhibits certain key signals that induce these changes? Alternatively, could this be due to time differences in phosphorylation signals, such as what was already seen for mTOR (24)?

It would be interesting to explore these questions in future studies, for example by mapping subclass-specific phosphorylation signalling in the cell, and also study the effects of IgA1 and IgA2 in FcαRI-KO and in Fcα/μR-KO macrophages, as these (CD89 and CD351 respectively) are the only currently known receptors able to bind IgA. Furthermore, it is fundamental to take into account that mice have a different expression pattern of Fc receptors than humans. Especially when it comes to IgA, unlike humans, mice do not express a homologue of the FcαRI (25–27). Therefore, not only is it important to explore these questions within a specific cell type (e.g. FcR signalling in macrophages vs DCs), but it is also crucial to do it within an appropriate physiological context, for example by using human cells or humanized mouse models.

Lipid Metabolism and Its Autocrine and Paracrine Effects

While part of this thesis was focused on intrinsic lipid metabolism, it is important to also keep in mind that lipids and lipid-metabolism-derived molecules also play very important roles in cell messaging, both in a paracrine as well as an autocrine fashion. A key enzyme involved in this process is COX2.

In **chapters 3-5**, the data showed that cells undergo different metabolic reprograming and acquire distinct metabolic phenotypes depending on the signal and cellular context of the pro-inflammatory stimuli. However, despite this, there seems to be a convergence towards COX2 upregulation and the synthesis of lipid mediators. As seen in **chapter 4**, IgA2 induced a hyper-inflammatory state in macrophages that was dependent on ATP Synthase activity, but also on COX2 expression. This was correlated with increased production of lipid mediators downstream of COX2, especially PGE_2. While PGE_2 is a well-known factor linked to inflammatory responses, it does not seem to be required for IgA2-driven potentiation of inflammation, since supplementing cells after COX2 inhibition with PGE_2 did not rescue the effects of IgA2. However, since the net effects of PGE_2 signalling are dependent on a number of factors, such as timing, concentration and duration of the stimulus, a potential contribution of PGE_2 to the proinflammatory effects of IgA2 stimulation cannot be totally ruled out yet. Since COX2 is crucial for the synthesis of many lipid mediators, including PGE_2, one could speculate that perhaps other immunomodulatory COX2 products, such as $PGF_{2\alpha}$, TxA_2, or PGI_2, (28–32) are contributing to, or even responsible for, this effect. This warrants further study.

Additional work highlighting the importance of COX2-dependent mediators in cellular function was shown in in **chapter 5**. While DCs require PGE_2 production and subsequent autocrine signalling to induce a Th2 inflammatory response following stimulation with *S. mansoni* egg antigens, they also require other COX2-dependent lipid mediators to ensure a proper Th1 response to LPS. Indeed, this was evidenced by the fact that general COX inhibition in DCs with indomethacin affected both Th1 and Th2 priming, while targeted mPGES inhibition mostly affected Th2 priming.
It is, therefore, interesting to note that while there is a central role for COX2 in supporting both type 1 and type 2 immune responses in macrophages and DCs, these cells are not dependent on the same COX2-dependent mediators, i.e. IgA-driven type 1 inflammation in macrophages being independent of PGE_2, while type 2 inflammatory responses by DCs, in the context of helminth infections, are specifically PGE_2-dependent.

Bridging Findings From Fundamental Studies to Clinical Implications

These studies highlight the importance of the contributions of metabolic programs and lipid mediators to immune cell function are highly in cell- and context-specific and advocate, for design of tailored targeting approaches of these processes to influence immune responses for future therapies. While IgG-dependent pathologies might benefit from targeted modulation of glycolysis, PPP and/or FA synthesis in macrophages, IgA-dependent pathologies, specifically IgA2, might instead benefit from a two-pronged strategy, by targeting glycolysis in DCs on one hand (1), and mitochondrial metabolism in macrophages on the other, thus ensuring the most optimal outcome to reign in uncontrolled inflammation.

These data also open interesting additional exploratory paths for the design of immunometabolic therapies. If inhibiting the aforementioned metabolic pathways in IgG- and IgA-dependent pathologies could be beneficial in curtailing unchecked inflammatory responses, it is tempting to speculate the opposite approach may also be possible: could inflammatory responses be improved by boosting these pathways in the context of immunocompromised patients, immune-evasive pathogens, and antibiotic-resistant infections, as host directed therapy? Could glycolysis and/or mitochondrial respiration be hyperactivated in situations where there are issues with mounting a robust protective inflammatory response to pathogens?

While it is an interesting idea to explore, its conceptualization presents as a hurdle. While genetic approaches to overexpress certain key enzymes to increase metabolic flux for specific pathways work well *in vitro*, their applicability in an *in vivo* setting would be highly complex, if not impossible. One alternative could be the use of allosteric regulators that are known to increase metabolic flux, such as Fructose-2,6-bisphoshphate (F-2,6-P_2) for glycolysis and AMP, NAD+, CoA and/or lactate in the case of oxidative phosphorylation/ATP synthase activity. Another strategy could be to use drugs that have been shown to activate pathways, be it directly or indirectly, such as the HIF-1α stabilizer BAY 85-3934, to boost glycolysis, or the fatty acid synthesis activator GGTI-298. Additionally, while targeted delivery of these compounds poses an issue, the recent use of liposomes to deliver drugs and metabolites to specific cells (33) could be exploited in the context of metabolic manipulation, to specifically deliver pathway activators and/or inhibitors to the target cells (e.g. macrophages, DCs, Th cells), to ensure an optimal immune response for each distinct context. For instance, therapies that involve the use of monoclonal IgG could be used in tandem with F-2,6-P_2/ BAY 85-3934 and GGTI-298, to respectively boost glycolysis and FA synthesis in macrophages, while AMP, NAD+, CoA and/or lactate could be used to increase ATP

Synthase activity and help in boosting the IgA-driven response by macrophages. Indeed, some metabolic activators have already been used in a pre-clinical context. For example, dichloroacetate, an activator of the Pyruvate Dehydrogenase Complex, which promotes oxidation of glucose derived pyruvate in the mitochondria, has been used in macrophages to improve anti-tumour immunoreactivity (34).

Finally, in the case of macrophages we found that certain IgG- and IgA-driven inflammatory responses were dependent on certain metabolic pathways, while with DCs we found that type-2 immune responses rely on PGE_2. As such it would be interesting to see if this could be applied in future therapies, such as in supplementing anti-parasitic vaccines with PGE_2 to ensure a more robust induction of type 2 immunity, thus potentially avoiding the immune-evasive mechanisms of parasites. Alternatively, PGE_2 could be inhibited as a way to downregulate uncontrolled type 2 responses, such as in the cases of asthma and allergy, provided this principle applies to other type 2 diseases. As type 1 responses are inhibited by type 2 responses, this means that specifically inhibiting PGE_2, while leaving other COX2-dependent mediators intact, could potentially induce a more robust type 1 inflammatory response, which could be beneficial in cases such as cancer or vaccines against bacteria and viruses. However, it is important to take into account any off-target effects of PGE_2 that could potentially affect cells other than DCs. For instance, induction of PGE_2 synthesis in macrophages was shown to impair Th2 responses during helminth infections (35). Therefore, it is crucial to develop therapies that are not only disease-specific but also cell-specific, to ensure the most efficient outcome.

Future Perspectives

Metabolism of the lipidome and its wide range of functional roles in shaping innate immune system is only starting to be uncovered. One conclusion that can be taken from the work done in **chapters 3**, **4**, and **5**, is that changes in cellular metabolism are highly context- and cell-dependent. As such, to bolster our arsenal of therapies against infection and/or inflammation, it is important to have a closer look at cellular immunometabolism and, particularly, lipid metabolism. Recent advances in the field of lipidomics (36–38) have opened the door to perform single-cell lipidomics, thus being able to better unravel the heterogeneity in immunometabolic phenotype of diverse and rare immune cell populations. It would be interesting to pair this new approach with spatial lipidomics (39–41) to get a better picture of the lipidome of specific cells/cellular populations but also their distribution within the tissue/milieu, as the immediate environment of a cell will be an important a factor in shaping its metabolism and subsequent activation state.

Furthermore, while this thesis is focused on lipid metabolism and lipid mediators, it also begs a question that has been gaining more and more relevance in our day and age – What are the immunological implications of whole body lipid imbalance, such as what is seen in obesity (42–44) and type 2 diabetes (45,46)? What about localized lipid abnormalities, such as those seen in the tumour microenvironment (TME) (47–49)? It is known that obesity is a risk factor for the development of cancer and pathologies associated with chronic inflammation, such as Alzheimer's or rheumatoid arthritis (50–52). It is also associated with impaired immune protection against infectious diseases, as clearly evidenced with the recent COVID19 pandemic (53). Obesity is a result of long-term intake of excessive calories, which results in increased accumulation of lipids in the liver and adipose tissue (54,55). Due to drastic diet and lifestyle changes in modern society, and the widespread availability of high-fat/calorically dense foods, obesity is on the rise, having been declared a global epidemic by the World Health Organization (56,57). It has been suggested that the expansion of adipose tissue due to prolonged intake of excess calories could cause hypoxia and mechanical stress to adipose tissue macrophages (ATMs), subsequently inducing inflammation and apoptosis (58). Not only is this conducive of inflammation within the adipose tissue itself, but it also leads to foam cell formation, due to efferocytosis of dead ATMs, thus contributing to further tissue dysfunction (59). Additionally, dietary fatty acids, particularly saturated fatty acids (SFAs), have been shown to skew ATMs towards a proinflammatory phenotype (60,61). During homeostasis, ATMs are somewhat metabolically inert, presenting low rates of both glycolysis and OXPHOS (62). However, ATMs from obese mice fed with a high-fat diet and exposed to SFAs were shown to have increased rates of glycolysis, and OXPHOS, and an accompanying proinflammatory phenotype (62–64).

Notably, there have been studies connecting obesity and adipose tissue dysfunction with arthritis. A recent study (65) showed that ACPAs lead to defective differentiation of adipocytes, promote M1 differentiation of macrophages, and increase inflammatory cytokine production. Moreover, cohort studies have suggested that obesity increases the chance of developing RA (66–70). Furthermore, it has already been extensively reviewed (71,72) that the AT can secrete molecules (i.e. adipokines) that increase inflammation and impair anti-RA therapies. Curiously, it has been hypothesized that this impairment, particularly when it comes to anti-TNF therapies, is due to increased Fc-receptor expression in omental adipocytes (71,73,74). As such, building on the work done in this thesis and further investigating the interplay between inflammation, antibody signalling, and lipid dysfunction, might prove invaluable in helping to find new strategies to tackle antibody-driven chronic inflammation.

In addition to obesity, lipid metabolism in myeloid cells also plays an important role in cancer. It is well known that tumour-associated macrophages (TAMs) are

characterized by having high expression of lipid transporters, such as CD36, and fatty acid binding proteins (FABPs), which results in increased fatty acid (FA) uptake and lipid accumulation in the cytosol (75,76). It has been described that tumour-derived lipid mediators, namely PGE_2, are capable of inducing an M2-like/tolerogenic phenotype in macrophages (77–79). Moreover, recent studies have shown that tumour-derived FAs, particularly monounsaturated long-chain FAs, induce an immunosuppressive phenotype in TAMs (76). Furthermore, it has been shown that lipid-laden TAMs display increased expression of immuno-inhibitory proteins, such as PD-L1, and decreased phagocytosis, therefore presenting a defective anti-tumour function (80). Additionally, it is already known that lipid-laden macrophages express high levels of PPARy, which can increase the expression of CD36 and lead to further lipid uptake (81,82), thus possibly creating a positive feedback loop that boosts the immunosuppressive phenotype in TAMs. Interestingly, there have been quite some anti-tumour strategies dependent on FcR signalling in TAMs, which work by overcoming their immunosuppressive phenotype and "kick starting" their inflammatory response. Indeed, these studies showed that using therapeutic antibodies against "don't eat me" signals, in conjugation with M1-derived exosomes, resulted in FcRs in TAMs binding to the Fc portion of the aforementioned therapeutic antibodies, leading to repolarization of TAMs, along with antibody-dependent cytotoxicity and antibody-dependent phagocytosis of tumour cells (83–85). However, to what extent this boosting of TAM inflammatory potential is dependent on metabolic reprogramming remains an open question.

Likewise, similar findings have been made in regard to tumour-associated DCs (TADCs). A recent study showed that tumour-derived PGE_2 induces cDC1 dysfunction and impairs anti-cancer T cell responses (86). It has also been suggested that TADCs develop a tolerising phenotype by uptaking FAs in the TME (87). TADCs upregulate several FA scavenger receptors, such as FABP4 and CD204, and display high lipid content and lipid-droplet accumulation (88–90). These TADCs were shown to have impaired Ag presentation and T cell priming abilities. Moreover, lipid droplet content in TADCs was shown to differ from non-TADCs, whereby TADC lipid droplets exhibit higher levels of oxidized polyunsaturated fatty acids (91,92), which has been suggested to impair cross-presentation by TADCs and subsequent priming of anti-tumour T cells (93). Furthermore, anti-tumour vaccination strategies relying on DC FcR signalling, although limited, have been proposed and tested in a clinical trial setting (94,95).

In conclusion, this thesis contributes to the growing recognition of the importance of lipid metabolism and Fc receptors in macrophage and DC biology, in the context of autoimmunity, chronic inflammation, cancer, obesity, and infection. Therefore, studying the effects of lipid mediators, FcR signalling, and the baseline immunometabolic

phenotype of tissue-associated myeloid cells in the context of each disease, in tandem with the aforementioned lipidomics tools, could give us an insight into the mechanism underlying the cause of these pathologies, help predict disease development and progression, and potentially lead to new therapies to prevent, treat or cure these diseases.

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