Modulating the behaviour of pancreatic tumour cells

Vlecken, D.H.W.

Chapter 6: Discussion

Danielle Vlecken

Causal determinants in Pancreatic cancer

In this study, two groups of genes were subjected to analysis. Genes that function in motility were assessed as well as genes that function in development were shown to be involved in altering cancer cell behaviour. It is obvious that many more groups of genes are potentially involved in tumour progression. Other genes have already been identified as key players in cancer. All genes, pathways and interactions involved, makes it difficult to predict the patient's disease profile, and the complexity (plus individual differences) makes it even more complicated to generate a custom made cure.

The two most important groups of genes participating in tumour genesis and –progression are the tumour suppressor genes (loss thereof) and oncogenes (overexpression or constitutive activation thereof) (Stan S.D. et al., 2010; Li L. and Leung P.S., 2014). One of these oncogenes is called RAS. In pancreatic cancer especially RAS is upregulated which leads to excessive cell division and tumour growth in the affected cells. Additionally, the Hedgehog (HH) canonical signalling pathway is activated in stromal cells. This results from upregulation of the developmental gene Hedgehog in pancreatic cancer. Also, two additional major pathways important in embryonic development, Wnt-βcatenin and Notch were found to be upregulated in pancreatic cancer (Morris IV JP. et al., 2010; HH. Wong and NR. Lemoine, 2009). All genes mentioned above have functions related to migration or adherence.

Micro-RNAs are approximately ~22 nucleotides in length. They are processed from hairpin forming precursor transcripts and function in posttranscriptional gene silencing by translational repression and promotion of target mRNA decay. These molecules were shown to play an important role in many malignancies (MiR-10b is important for breast cancer for example and MiR-10a is of importance for pancreatic cancer. Targeting these molecules could be feasible strategy to fight malignancies. MiR-10a was identified as a facilitating factor repressing HOX B1 and HOX B3. Repression of MiR-10a was shown to inhibit metastasis and invasion. (Marques I., et al., 2008; Khan S. et al., 2013). If simultaneous retinoic acid receptor antagonists are used, these processes are completely abolished.

Malignant disease control

Pancreatic cystic neoplasms are detectable at present day with a biomarker called CEA, on the other hand, pancreatic adenocarcinoma is difficult to detect, while this form accounts for 90% of the cases. For the only biomarker, CA19-9 which is based on ancillary testing, that is available for early detection of pancreatic cancer is not specific for the pancreas but could also point to the bile

bladder, however, this test was reported to be suitable for detection of recurrent adenocarcinoma. Pancreatic cystic cancers can be detected when cystic fluid is taken out (Melton S.D. et al., 2010)

Tumour resection is currently a widely used procedure to treat people with malignant, but also with metastatic disease. This method is generally accepted because the patient acquires then a survival benefit. However for pancreatic metastases is this treatment extremely ill-defined (Adler H., et al., 2013)

Recent concepts

Novel treatments and anti-cancer compounds are being evaluated at present as alternative treatments for cancer. One of these concepts was displayed in Chapter 5: biological or organic compounds such as snake venoms. Also herbs are currently under investigation and it was reported that vegetable and fruits for example are able to have a tumour regress (Stan S.D., et al., 2010; Li L. and Leung P.S., 2014; Hendrix M.J.C. et al., 2007)

Recent studies also include assessment of protein trafficking by virus induced nanoparticles into human cells (Mangeot PE. et al., 2011). For instance to target medication to a specific structure in the human body. As is shown in this work, anti-malignant metal compounds are functional against common carcinogenic processes like angiogenesis. However, if such compound would be used by a patient without a proper delivery system, the patient's healthy cells would be the first to die. Nanoscale cancer vaccines are in development presently. These contain exosomes which are loaded with tumour antigen so that antigen presentation takes place through dendrocytes to effector cells. Then NK cells can recognize the tumour by the antigen it expresses, and target it (Tan A. et al., 2012; Zeelenberg IS., et al., 2008). On the other hand, exosome signalling was reported to be abundant in cancer. Such particle is capable of loading itself with oncogenic cargo in order to empty itself after merging with the recipient cell membrane (Lee T.H. et al., 2011).

Concluding remarks

As might have been made clear in this work, most cancers originate from damaged or irritated tissue which, over the course of years or decades might adapt to the new (irritable) microenvironment. If such cells do not die or are not removed by the organismal defence mechanismsthey will become adapted and are able to prosper and ultimately will progress into a malignant tumour. It is widely known that nutrition determines physiologic and pathologic processes and recently it was even reported that by altering the tumour microenvironment (by changing diet), the tumour could degenerate (Hendrix MJC. et al., 2007). It is therefore essential to include whole animal models in

cancer studies. In this work I have demonstrated that zebrafish larvae are extremely useful as a model for studying cancer progression and to delineate the properties of potential anti-cancer drugs.

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