An Odyssey towards personalised medicine in breast cancer

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2018

document version
Publisher's PDF, also known as Version of record

ENGLISH SUMMARY

The goal of personalised medicine is to tailor therapies to the genetic information of a patient to optimise the effectiveness and safety of the treatment on an (almost) individual level. This thesis describes one of the many odysseys taken in science and medicine towards achieving that goal.

Chapter 1 explains that personalised medicine is essential for breast cancer, as this is a highly heterogeneous disease. It elaborates on the aggressive HER2+ breast cancer subtype where therapy resistance is common, which is linked to the disease's heterogeneity. Chapter 1 then introduces the tool that was used in this thesis to identify oncogenic drivers of breast cancer: Mouse Mammary Tumour Virus (MMTV)-induced insertional mutagenesis. Several novel MMTV-targets and thus candidate (proto-)oncogenes were identified. This thesis focusses on those genes that play an activating role in the PI3K/AKT/mTOR pathway: *Eras*, *Irs4*, and to much lesser extent, *Igf2*.

Chapter 2 presents the results of MMTV-mediated insertional mutagenesis screens aimed at the identification of genes and genetic pathways playing a role in HER2+ breast cancer. It identifies the *Eras* locus as significantly more targeted by MMTV in tumours from the HER2+ breast cancer mouse models compared to wildtype mice. Chapter 2 confirms *ERAS* as an oncogenic driver upon expression and verifies that it is expressed in human HER2+ breast cancer (in 12-27% of cases). It also reveals that ERAS synergistically accelerates cell proliferation and tumorigenesis with ERBB2 (HER2). Additionally, chapter 2 describes that ERAS constitutively hyperactivates the PI3K/AKT/mTOR pathway and, by doing so, functionally replaces ERBB3, which is normally the activator of this pathway in HER2+ breast cancer.

Chapter 3 identifies *Irs4* as an MMTV target and confirms it as a mammary oncogene. IRS4 is shown to potently activate the PI3K/AKT/mTOR pathway, independent of any upstream activation, and to be insensitive to the SHP2-mediated deactivation that is common for IRS proteins, thus leading to its sustained signalling.

Chapter 3 further identifies the absence of a SHP2-binding domain in IRS4 as the underlying mechanism of the latter. It shows that IRS4 is mainly expressed in HER2+ breast cancers, as well as triple negative subtypes, whereas only scarcely in the luminal A or B subtypes.

Chapter 4 highlights a strong synergism towards tumorigenesis between *IRS4* expression and *ERBB2* overexpression, as was shown for *ERAS* expression in chapter 2. Chapter 4 also reveals that expression of *ERAS* or *IRS4* greatly reduces the sensitivity to the HER2-targeting drugs Trastuzumab and Lapatinib in cancer cells *in vitro* and human xenografts *in vivo*. Evidence for a potential role for both genes in acquired therapy resistance is also presented. Chapter 4 confirms the hyperactivation of the PI3K/AKT/mTOR pathway by ERAS or IRS4 as the underlying mechanism for their induction of therapy resistance, suggesting inhibition of this pathway as a potential therapeutic avenue.

Chapter 5 sets the findings of this thesis in a broader perspective, including considerations for personalised medicine. It discusses potential treatment options for resistant HER2+ breast cancer, in particular in the context of tumours with a hyperactivated PI3K/AKT/mTOR pathway. Chapter 5 also presents hypotheses on the mechanisms of transcriptional repression of *ERAS*, *IRS4* and *IGF2*, and their upregulation in breast cancer. The roles of the three genes in embryonic development and stem cells is discussed in relation to cancer, which warrants further research. Chapter 5 further discusses the technical and practical benefits of MMTV-mediated insertional mutagenesis over other screening tools, among others that MMTV is by far the least biased tool. It concludes that this is a highly valuable tool to study the clinically relevant heterogeneity in breast cancer, to advance the next odysseys towards personalised medicine.