Development and application of a patient-derived xenograft platform to test anti-cancer agents

Akademisk avhandling

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Avhandlingen baseras på följande delarbeten

I. Melanoma patient-derived xenografts accurately model the disease and develop fast enough to guide treatment decisions

II. Hypoxia-regulated gene expression explains differences between melanoma cell line-derived xenografts and patient-derived xenografts
Oncotarget. 2016 Apr 26;7(17):23801-11

III. TH1579 (Karonudib) inhibits MTH1 and microtubule dynamics and has broad anti-melanoma effects in patient-derived xenografts

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Development and application of a patient-derived xenograft platform to test anti-cancer agents

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Abstract

Malignant melanoma is the most aggressive form of skin cancer and incidence rates are on the rise. Despite recent improvements in treatment options, the disease still remains lethal. Which calls for expedited solutions. In this thesis I will discuss three studies, which have not only contributed new knowledge to the research community but also led to development of tools used in cancer research.

In the first paper we developed a platform of patient-derived xenografts (PDXes) from metastatic melanoma patients. We show that PDXes can accurately predict clinical treatment responses and that the xenografts can be established in time to benefit the patients. Thus, the platform can be used for multiple pre-clinical and clinical purposes.

In the second paper we compared the transcriptome of cell line-derived xenografts (CDXes) and PDXes. The initial aim was to investigate if CDXes would be transcriptionally similar to PDXes and could therefore be used as in vitro surrogates for the PDXes. Instead, we identified a significant transcriptional difference between CDXes and PDXes, mainly explained by the pseudo hypoxia experienced by the cell lines once they are transplanted to the physiological environment.

In the third study, we ran a pre-clinical trial in malignant melanoma PDX mouse models with the aim of identifying a predictive biomarker of the MTH1 inhibitor, Karonudib. By comparing the genomic and transcriptomic profiles of the responding and non-responding PDXes we identified that Karonudib has cytotoxic effect independent of those profiles. Also, we discovered that Karonudib causes cytotoxic effect beyond MTH1 inhibition.

Taken together, our data shows that PDX models predict clinical responses and can be used to test drugs pre-clinically, and argues that pre-clinical testing in PDX models is superior to cell line based drug testing.

Keywords: Malignant melanoma, patient-derived xenografts, MTH1, Karonudib, pre-clinical research.