Immunological effects of isolated regional perfusion in malignant melanoma

Malignant melanoma patients with metastatic disease confined to the limbs or liver may be treated with hyperthermic isolated limb perfusion (ILP) or hyperthermic isolated hepatic perfusion (IHP) with high dose melphalan. Following ILP and IHP tumours gradually decrease in size during several months, which might be explained by a treatment-induced immunological anti-tumour effect. This thesis aimed at investigating the potential role of the immune system for treatment response to ILP and IHP by analyses of patient material and the usage of in vitro models. It was seen that melanoma patients who harboured a high fraction of activated and antigen-specific cytotoxic $CD8^+$ T cells in blood and in tumours prior to ILP and IHP were more likely to have a longer progression-free survival and to achieve a complete disappearance of tumours after treatment. Furthermore, it was revealed that a short-term exposure of melanoma cells to melphalan, as in a perfusion setting, increased the fraction of intermediate and non-classical monocytes and caused an activation of T cells. Additionally, the procedure enhanced the production of chemokines and the expression of chemokine receptors on lymphocytes, thus likely facilitating the recruitment of immune effector cells into tumours. These observations may be due to a melphalan-induced upregulation of immune-related stress markers on melanoma cells and a release of immunostimulatory molecules such as danger associated molecular patterns. In conclusion, the findings presented in this thesis point towards a role of the immune system for treatment responses following both ILP and IHP, suggesting that it may be beneficial to combine isolated regional perfusion with immunotherapy.

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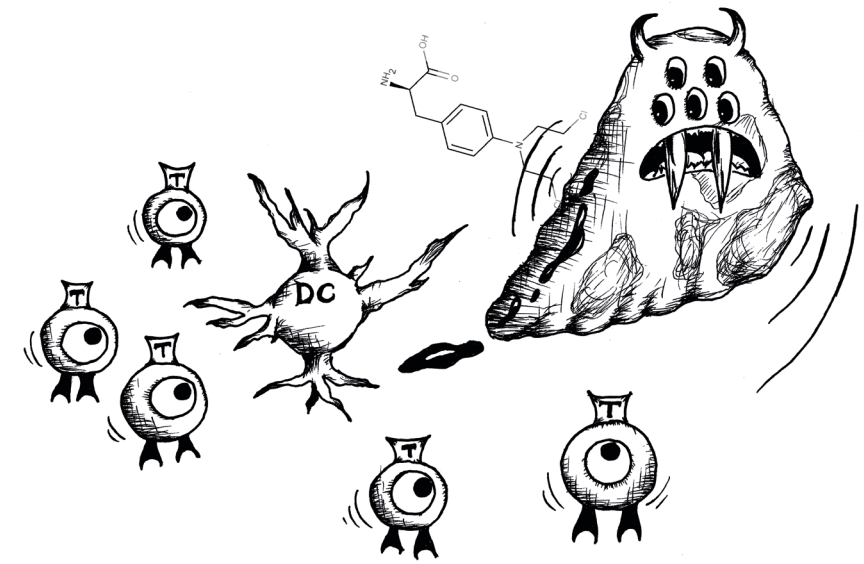

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