Immunological effects of isolated regional perfusion in malignant melanoma

Akademisk avhandling

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Immunological effects of isolated regional perfusion in malignant melanoma

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Abstract

Malignant melanoma patients with metastatic disease confined to the limbs or liver may be treated with hyperthermic isolated regional perfusion with a chemotherapeutic agent, most commonly melphalan. This procedure enables much higher tissue concentrations of the chemotherapeutic agent compared with systemic administration. Isolated limb perfusion (ILP) is approved for treatment of cutaneous metastatic melanoma, while the efficacy of isolated hepatic perfusion (IHP) is under evaluation for the treatment of liver metastases from uveal melanoma. Following ILP and IHP tumours often gradually decrease in size during a period of several months, which might be explained by a treatment-induced immunological anti-tumour response. This thesis aimed at investigating the potential role of the immune system for treatment response to ILP and IHP utilising in vivo analyses of patient material and mice models and in vitro cell cultures. As reported in Paper I and Paper II, patients who harboured a high fraction of activated and antigen-specific T cells in blood prior to ILP were more likely to achieve a complete disappearance of tumours following ILP. Furthermore, the in vitro and in vivo assays showed that melphalan exposure enhanced the activation of T cells and increased the numbers of intermediate and non-classical monocytes. This may be due to the melphalan-induced upregulation of immune-related stress markers on melanoma cells, which in turn stimulated immune cells. In Paper III it was reported that high levels of interferon-stimulated gene products in patient blood, including CXCL10, CCL2 and PD-L2, were predictive of a favourable treatment response to ILP, and that the receptors of these ligands increased on immune cells following treatment. Paper IV describes different T cell immune profiles in blood between uveal melanoma patients and healthy controls, and showed that melanoma patients harboured a lower frequency of CD8+ T cells and more regulatory T cells. Uveal melanoma patients achieved a longer progression-free survival following IHP if they harboured a high fraction of activated T cells in blood. 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.

Keywords: Melanoma, isolated regional perfusion, ILP, IHP, melphalan, immunogenic cell death, T cells, monocytes, ISG

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