Immunological effects of isolated regional perfusion in malignant melanoma

Akademisk avhandling

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av **Junko Johansson**

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Avhandlingen baseras på följande delarbeten:

I. **Johansson, J.**, Kiffin, R., Andersson, A., Lindnér, P., Naredi, P., Olofsson Bagge, R. and Martner, A. Isolated Limb Perfusion With Melphalan Triggers Immune Activation in Melanoma Patients.
Frontiers in Oncology, 2018, 8(570)

II. Martner, A., **Johansson, J.**, Ben-Shabat, I. and Olofsson Bagge, R. Melphalan, Antimelanoma Immunity, and Inflammation—Letter.
Cancer Research, 2015, 75(24)

III. **Johansson, J.**, Kiffin, R., Aydin, E., Nilsson, M.S., Hellstrand, K., Lindnér, P., Naredi, P., Olofsson Bagge, R. and Martner, A. Isolated limb perfusion with melphalan activates interferon-stimulated genes to induce tumor regression in patients with metastatic melanoma.
Submitted

IV. **Johansson, J**., Kiffin, R., Siarov, J., Mölne, J., Naredi, P., Olofsson Bagge, R., Martner, A. and Lindnér, P. Presence of activated T cells in peripheral blood correlates to longer progression-free survival in patients undergoing isolated hepatic perfusion for uveal melanoma liver metastasis.
Manuscript

SAHLGRENSKA AKADEMIN
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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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