

Tumor metastasis – mechanisms and prevention

Akademisk avhandling

som för avläggande av medicine doktorexamen vid Sahlgrenska akademien,
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av **Sanchari Paul**

Fakultetsopponent:
Docent Stina Wickström
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Avhandlingen baseras på följande delarbeten

- I. Arabpour M, **Paul S**, Grauers Wiktorin H, Kaya M, Kiffin R, Lycke N, Hellstrand K, Martner A. An adjuvant-containing cDC1-targeted recombinant fusion vaccine conveys strong protection against murine melanoma growth and metastasis. *Oncoimmunology*. 2022 Aug 24;11(1):2115618.
- II. **Paul S**, Kaya M, Johnsson O, Grauers Wiktorin H, Törnell A, Arabpour M, Hellstrand K, Martner A. Targeting murine metastatic cancers with cholera toxin A1-adjuvanted peptide vaccines. *Submitted*
- III. Kaya M, Johnsson O, **Paul S**, Issdisai N, Dongre A, Hellstrand K and Martner A. NRF2 activation by myeloid cell-derived oxidative stress induces SNAI-driven EMT and metastasis in breast cancer. *Manuscript*

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Abstract

Metastatic spread of tumor cells accounts for the majority of cancer-related deaths. We have developed cancer vaccines based on the immunostimulatory adjuvant cholera toxin A1 (CTA1), including vaccines that deliver tumor antigens and CTA1 to cross-presenting type 1 conventional dendritic cells (cDC1). We also explored mechanisms of epithelial-mesenchymal transition (EMT), in which cancer cells acquire features that facilitate metastasis. **In paper I**, we used fusion vaccines that comprised of a cDC1-targeting anti-CD103 single-chain antibody (aCD103) and the CTA1 adjuvant fused with MHC class I and II-restricted epitopes from the model tumor cell antigen ovalbumin (OVA). The rationale was to deliver the antigen (OVA) and the adjuvant (CTA1) to highly efficient antigen-presenting cells (CD103-expressing cDC1) to achieve optimal induction of T cell-mediated immunity. This CTA1-I/II-aCD103 vaccine construct induced robust antigen-specific CD8⁺ T cell responses along with a Th17-polarized CD4⁺ T cell response and efficiently reduced primary growth and metastasis of B16F1-OVA melanoma in prophylactic and therapeutic settings. **Paper II** expanded these findings by demonstrating that CTA1-based cancer vaccines enhanced immune responses against the endogenous tumor-associated antigens TRP2 and Twist1 in mice. This led to significant protection against metastasis in B16F1 melanoma and 4T1 breast cancer models. **In paper III**, we explored the mechanisms underlying the induction of EMT, in which epithelial tumor cells acquire mesenchymal characteristics that facilitate metastatic spread. The results revealed that EMT, orchestrated by the induction of transcription factors such as SNAIL and SLUG, was triggered by reactive oxygen species (ROS), which mediate oxidative stress in the malignant microenvironment. The ROS-induced EMT led to metastasis of breast cancer *in vivo*, which could be mitigated through genetic and pharmacological inhibition of NOX2, a principal ROS-producing enzyme expressed by tumor-infiltrating myeloid cells. **In summary**, this thesis identified CTA1-based fusion vaccines that control the growth and dissemination of tumor cells and unveiled novel and potentially targetable mechanisms relevant to EMT-induced metastasis.

Keywords: cancer vaccines, adjuvant, metastasis, EMT, cDC1s, TAAs