

SINGLE-CELL SPATIAL IN SITU TRANSCRIPTOMICS UNRAVELS VULVAR HSIL COMPOSITION ASSOCIATED WITH COMPLETE RESPONSE TO THERAPEUTIC VACCINATION

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Background Vulvar High-grade Squamous Intraepithelial Lesion (vHSIL) is predominantly induced by high-risk Human Papilloma Virus type 16 (HPV16). In two independent trials, therapeutic vaccination against the HPV16 E6 and E7 oncoproteins resulted in objective partial and complete responses in half of the HPV16+ vHSIL patients at 12 months follow-up. Here, the pre-vaccination vHSIL tumor microenvironment in relation to the vaccine-induced clinical response was in-depth investigated.

Methods A unique novel high-plex spatial molecular imaging technique, CosMx (Nanostring), was applied, which for the first time allows the visualization of 1000 RNA transcripts at a subcellular resolution in situ on FFPE pre-immunotherapy tissue, using cyclic fluorescent in situ hybridization. This allowed both the discovery of new cell types in the tumor microenvironment of vHSIL, as well as the investigation of their spatial interactions. We studied a cohort of 20 pre-immunotherapy vHSIL samples, 6 complete responders, 7 partial responders and 7 non-responders. Data was analyzed with the R Giotto package for spatial transcriptomics, applying unsupervised clustering for cell identification and machine learning to unravel spatial patterns in the tissue.

Results The tumor microenvironment of complete responders is characterized by the presence of distinct pro-inflammatory dendritic cells, macrophages and T cells, whereas these cells are scarce in non-responders. Moreover, also the spatial composition of these patient groups differed significantly, the tumor microenvironment of complete responders harbors direct spatial interactions between pro-inflammatory innate and adaptive immune cells indicating an adequate ongoing anti-tumor immune response, which is lacking in non-responders.

Conclusions Single-cell in situ transcriptomics identified the key importance of multiple pro-inflammatory immune cell types for response of vHSIL to therapeutic vaccination, as well as the importance of the spatial organisation of these immune cells in order to be able to execute their pro-inflammatory function. This indicates that a well coordinated immune response on multiple levels, i.e. having sufficient numbers of both pro-inflammatory myeloid and lymphoid cells, as well as their spatial architecture, is pivotal for successful response to immunotherapy.

Ethics Approval Ethics approval was provided by the Leiden University Medical Center. Patients were included in this study after providing written informed consent. This study was conducted in accordance with the Declaration of Helsinki and in accordance with Dutch law.

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