Quantitative analyses of the in situ cellular immune response in cervical squamous cell carcinoma

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ABSTRACT

This PhD dissertation was carried out at Department of Oncology, Aalborg Hospital, Department of Pathology, Aalborg Hospital, and Stereology and Electron Microscopy Laboratory and MIND Center, University of Aarhus.

The aim of the dissertation was to study the in situ cellular immune response towards cervical cancer. Three studies were conducted.

The aim of the first study was to present a method to obtain basic biological data of the in situ cellular immune response towards cancer. Using stereology, we estimated the 2D density and frequency of immune cells of 10 different phenotypes in cone biopsies from 20 patients with FIGO stage I cervical squamous cell carcinoma. The anatomical distribution of immune cells with respect to intraepithelial, periepithelial or stromal compartments was recorded in normal epithelium, dysplastic epithelium and carcinoma.

We found more immune cells to be present in cancer than in dysplasia and normal epithelia. A median total number of 278×10^3 CD3+, 69.1×10^3 CD4+ and 113×10^3 CD8+ cells were present in the cancers. A median number of 63 CD3+, 11 CD4+ and 29 CD8+ cells were present per cancer cell. The method was found to be usable and of value in clinical pathological research.

The purpose of the second study was to investigate differences in the primary in situ cellular immune response between patients with and without relapse of stage IB cervical squamous cell carcinoma. Using the method presented in the first study, paraffin-embedded tissue from 40 patients (20 with and 20 without relapse) was evaluated. Sections were immunostained for CD1a+, CD3+, CD4+, CD8+, CD20+, CD45RA+, CD45RO+, CD57+, CD68+ and GrB+ cells.

We found significantly lower densities of CD3+, CD4+ and CD8+ cells (both intra- and peritumoral) in tissue from patients who had relapse. Also densities of intratumoral CD1a+ and CD57+ cells and peritumoral CD20+, CD45RA+, CD45RO+ and CD57+ cells were significantly lower among patients with relapse.

To validate further the results found in Study II, a cohort study including 102 patients treated for cervical squamous cell carcinoma stages IB and IIA was performed. The in situ cellular immune response was investigated with respect to densities of T cells (CD3+), T helper/regulatory cells (CD4+) and cytotoxic T cells (CD8+) in intra- and peritumoral tissue.

We found that an increase in the density of both CD3+ and CD8+ cells decreased the risk for relapse of disease. The decrease in hazard ratio was highly significant for both intra- and peritumoral cells. The largest decrease in hazard ratio was found for peritumoral CD3+ cells, which was 0.27 on increasing the cell density from 795 to 2,043 cells/mm^2 (25 to 75 percentile). According to this study, low density of particularly peritumoral CD3+ cells is associated with increased risk of relapse in squamous cell cervical cancer.