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Immune-related transcriptional landscape of breast cancer in the context of its dissemination

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ABSTRACT

Metastatic disease remains the leading cause of cancer-related deaths. Metastasis is a multistep process that involves the action of both tumour cells, and the surrounding tumour microenvironment, which is composed of normal cells, including cells of the immune system. In addition, metastasis is facilitated by both direct and indirect interplay between cancer cells and components of the blood, e.g., platelets, plasma or plasma cytokines. The subject of the presented work is breast cancer – the most frequently diagnosed neoplasm among females, and its dissemination. Better understanding of molecular mechanisms of cancer metastasis and the involved crosstalk between the tumour and its microenvironment is crucial for development of new methods of its diagnosis, relapse risk assessment, and treatment.

My PhD thesis is a cycle of four original research papers describing the changes of immune-related transcriptome of breast cancer in the context of various aspects of its dissemination. The analyses were performed on archival tissue material, comprising primary tumours and lymph node metastases, of patients with known status of nodal involvement and circulating tumour cells. The immunotranscriptome of archival material, generated using nCounter technology (NanoString) – the golden standard gene expression approach for formalin fixed and paraffin embedded tissues, was subjected to thorough bioinformatic and statistical analysis.

The project aimed to determine immunotranscriptome profiles of: [1] primary tumours according to the phenotype of circulating tumour cells (mesenchymal vs. epithelial) present in blood; [2] primary tumours according to the platelet count (higher normal count, defined as above upper quartile of the normal range, vs. normal count – the remaining normal range); [3a] primary tumours that did not metastasise to lymph nodes according to their phenotype (mesenchymal vs. epithelial); [3b] primary tumours that metastasised to lymph nodes according to their phenotype (mesenchymal vs. epithelial); [3c] lymph node metastases according to their phenotype (mesenchymal vs. epithelial); [4] primary tumours vs. paired lymph node metastases – changes associated with lymphatic spread.

The obtained results indicate: [1] an increased expression of NF-kB signalling-related genes in primary tumours seeding mesenchymal circulating tumour cells; [2] an elevated infiltration of CD8+ T lymphocytes and resting mast cells and increased expression of genes coding for cytokines promoting thrombopoiesis, platelet activation and their pro-tumorigenic function – IL17A (IL17A), MDC (CCL22) and MMP1 (MMP1), in primary tumours of patients with elevated platelet count; [3a] a decreased expression of inflammatory response-related genes in mesenchymal primary tumours that did not metastasise to lymph nodes; [3b] an increased activity, plausibly also elevated infiltration, of antigen presenting cells in mesenchymal primary tumours that metastasised to lymph nodes; [3c] a decreased expression of genes involved in interferon production in mesenchymal lymph node metastases;

[4] a reduced expression of complement system-related genes in lymph nodes compared to matched primary tumours.

My studies provided new insight into the role of immune system in breast cancer dissemination. NF-kB signalling and the complement system seem to be crucial for metastasis formation, thus appear to be potent targets for anti-metastatic treatment. The stroma-induced thrombopoiesis also merits further investigation as it seems to promote the dissemination. The outcomes of my project may serve as a basis for development of novel therapeutic approaches dedicated for breast cancer patients.