Delineating cellular heterogeneity and organization of breast cancer stem cells

Akademisk avhandling

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Avhandlingen baseras på följande arbeten:


Delineating cellular heterogeneity and organization of breast cancer stem cells

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ABSTRACT

Breast cancer is characterized by a high degree of heterogeneity in terms of histological, molecular and clinical features, affecting disease progression and treatment response. The cancer stem cell (CSC) model suggests, that cancers are organized in a hierarchical fashion and driven by small subsets of CSCs, endowed with the capacity for self-renewal, differentiation, tumorigenicity, invasiveness and therapeutic resistance. The overall aim of this thesis was to characterize CSC phenotypes and the cellular organization in estrogen receptor α + (ERα+) and ERα- subtypes of breast cancer at the individual cell level. Furthermore, we aimed to identify novel functional CSC markers in a subtype-independent manner, allowing for better identification and targeting of breast-specific CSCs.

At present, single-cell quantitative reverse transcription polymerase chain reaction represents the most commonly applied method to study transcript levels in individual cells. Inherent to most single-cell techniques is the difficulty to analyze minute amounts of starting material, which most often requires a preamplification step to multiply transcript copy numbers in a quantitative manner. In Paper I we have evaluated effects of variations of relevant parameters on targeted cDNA preamplification for single-cell applications, improving reaction sensitivity and specificity, pivotal prerequisites for accurate and reproducible transcript quantification.

In Paper II we have applied single-cell gene expression profiling in combination with three functional strategies for CSC enrichment and identified distinct CSC/progenitor clusters in ERα+ breast cancer. ERα+ tumors display a hierarchical organization as well as different modes of cell transitions. In contrast, ERα- breast cancer show less prominent clustering but share a quiescent CSC pool with ERα+ cancer. This study underlines the importance of taking CSC heterogeneity into account for successful treatment design.

In Paper III we have used a non-biased genome-wide screening approach to identify transcriptional networks specific to CSCs in ERα+ and ERα- subtypes. CSC-enriched models revealed a hyperactivation of the mevalonate metabolic pathway. When detailing the mevalonate pathway, we identified the mevalonate precursor enzyme 3-hydroxy-3-methylglutaryl-CoA synthase 1 (HMGCS1) as a specific marker of CSC-enrichment in ERα+ and ERα- subtypes, highlighting HMGCS1 as a potential gatekeeper for dysregulated mevalonate metabolism important for CSC-features. Pharmacological inhibition of HMGCS1 could therefore be a novel treatment approach for breast cancer patients targeting CSCs.

Keywords: Breast cancer, cancer stem cells, cellular heterogeneity
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