

DOCTORAL THESIS

Cytotoxic dynamics of natural killer cell at the single cell level

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Abstract

Natural Killer (NK) cell, a crucial player of the human innate immune defense system, detects and kills virus-infected cells and cancer cells. Although the relevant molecular machineries involved in NK cell activation and NK-target cell interactions are largely known, how their collected dynamics regulate fast yet highly selective target cell killing in the complex environment of tissues is poorly understood. In traditional bulk killing assays, heterogeneity and kinetic details of individual NK-target cell interactions are masked, seriously limiting analysis of the underlying dynamic mechanisms. Therefore, the aim of my PhD study is to develop quantitative microscopy assays to elucidate, at the single cell level, real-time killing dynamics of epithelial cancer cells by primary NK cells purified from human blood. Results from my study not only identified the rate-limiting kinetics in NK-cancer cell interaction and mechanistically relevant heterogeneity in the process, but also characterized key molecular events and regulatory components of the NK cell machinery that were associated with the observed cytotoxic dynamics and heterogeneity. NK cells are considered promising candidate for cancer treatment, especially for eliminating residual cancer cells after conventional therapy. The fundamental knowledge acquired from my PhD study, in particular regarding how killing by primary NK cell varies between different target cancer cell types, provides new mechanistic insight that may help to develop this treatment strategy. And the quantitative microscopy assays that I developed are readily extendable to analysis of other cell-cell interaction dynamics, e.g., involved in cytotoxic T cell function.

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