

PROGRESS REPORT for Mizutani Foundation Research Grant

Reference Number: 220087

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Organization: Hebrew University

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Grant Title: Decoding heparan sulfate proteoglycans' essential role in cancer aggressiveness

Progress Report:

(a) Abstract:

Carcinomas often exhibit aggressive characteristics, such as enhanced migration abilities, through the execution of the epithelial-mesenchymal transition (EMT) program. Heparan sulfate (HS) is a polysaccharide expressed on the surface of aggressive cancer cells, which acts as a co-receptor to stimulate EMT-associated signaling pathways. However, despite HS' role in cancer aggressiveness, the mechanisms governing its EMT-dependent biosynthesis remains poorly understood. Here, we characterized the HS chain elongation enzyme, exostosin glycosyltransferase 1 (EXT1), as an essential component of the EMT



program. We identified an EMT-dependent expression of EXT1 and its selective upregulation in aggressive tumor subtypes and cell lines. Overexpression of EXT1 in epithelial cells is sufficient to induce HS biosynthesis, cell migration, and invasion, form tumors in mice, and activate the STAT3 pathway. Moreover, its knockout in aggressive cells significantly inhibited their EMT-associated characteristics. These findings demonstrate a cellular mechanism by which metabolic processes regulate signaling pathways to govern cell state.