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„The role of chitinase-3-like protein 1 in the pathobiology of gliomas”

Rozprawa na stopień doktora nauk medycznych i nauk o zdrowiu w dyscyplinie nauki medyczne

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Abstract

Chitinase-3-like protein 1 (CHI3L1) is a secreted, non-enzymatic glycoprotein that binds proteins and carbohydrates, and interacts with cell-surface and extracellular-matrix proteins, proteoglycans, and polysaccharides. Multiple interacting partners of CHI3L1 make the dissection of its functions challenging. While many studies reported an upregulation of CHI3L1 mRNA/protein in various tumors, its exact roles in tumorigenesis remain elusive. We performed a comprehensive analysis of *CHI3L1* expression in multiple public datasets including TCGA (The Cancer Genome Atlas) and single-cell RNAseq datasets to determine the cellular source of *CHI3L1* expression in gliomas. The highest CHI3L1 mRNA/protein levels were detected in glioblastoma (GBM), a highly malignant and diffusive brain tumor. We demonstrate that CHI3L1 knockout in human U87-MG glioma cells grossly affects transcriptional profile and *in vitro* invasiveness of these cells, and strongly reduces the growth of intracranial U87-MG tumors in athymic mice. Remarkably, CHI3L1 knockout in glioma cells resulted in normalization of tumor vasculature and diminished infiltration of glioma-associated myeloid cells. Mechanistically, CHI3L1 depleted cells had reduced MMP2 expression/activity, which was associated with reduced invasion, and downregulated osteopontin (SPP1), a crucial factor driving the myeloid cell accumulation in GBM. Altogether, the presented work demonstrates that CHI3L1 is a key player in GBM progression, and its targeting represents a novel strategy in therapy of GBM patients.