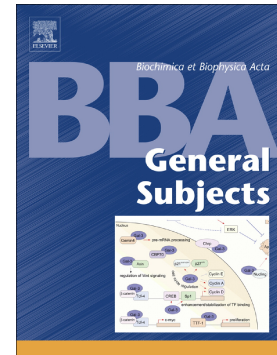


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Exostosin-like 2 regulates FGF2 signaling by controlling the endocytosis of FGF2

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Abbreviations: EdU, 5-ethynyl-2'-deoxyuridine; EXT, exostosin; EXTL, EXT-like; FGF2, fibroblast growth factor 2; GAG, glycosaminoglycan; GlcA, glucuronic acid; GalNAc, *N*-acetylgalactosamine; GlcNAc, *N*-acetylglucosamine; HS, heparan sulfate; MEF, mouse embryonic fibroblast; PBS, phosphate buffered saline; PG, proteoglycan.

Abstract

Background: Heparan sulfate proteoglycans are ubiquitously expressed on cell surfaces and in extracellular matrices, and are engaged in heparin-binding growth factor-related signal transduction. Thus, changes in the amounts, structures, and chain lengths of heparan sulfate have profound effects on aspects of cell growth controlled by heparin-binding growth factors such as FGF2. Exostosin glycosyltransferases (EXT1, EXT2, EXTL1, EXTL2, and EXTL3) control heparan sulfate biosynthesis, and the expression levels of their genes regulate the amounts, chain lengths, and sulfation patterns of heparan sulfate. Unlike EXT1, EXT2, and EXTL3, EXTL2 functions chain termination of heparan sulfate. Here, we examined the importance of EXTL2 in FGF2-dependent signaling.

Methods: We investigated heparan sulfate biosynthesis and FGF2 signaling using four cell lines, EXT1-deficient cells, EXT2-, EXTL2-, or EXTL3-knockdown cells, by HPLC, qRT-PCR, flow cytometry, and western blotting.

Results: Reduced expression of either EXT1, EXT2, or EXTL3 decreased heparan sulfate biosynthesis, and consequently suppressed the FGF2-dependent proliferation of mouse L fibroblasts. In contrast, although knockdown of *EXTL2* increased the amounts of heparan sulfate, FGF2-dependent proliferation was significantly inhibited because the increased heparan sulfate enhanced the incorporation of FGF2 into the cells.

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