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Abstract

Proteoglycans control numerous normal and pathological processes. During tumor development and growth, proteoglycan expression is markedly modified in the tumor microenvironment. Altered expression of proteoglycans in cancer cells affects cancer cell signaling, growth and survival, cell adhesion, migration and angiogenesis. Although serglycin has been initially characterized as intracellular proteoglycan present mainly in hematopoietic cells, recent data indicate that it is expressed by cancer cells and may be important for cancer cell biology. The biological role of serglycin in cancer remains unknown, therefore the aim of the present study was to investigate the expression and biological role of serglycin in breast cancer. We examined the effect of serglycin on breast cancer cell properties and phenotype. We also investigated the ability of serglycin to regulate complement system activity and osteoclastogenesis.

We showed the *in situ* expression of serglycin by breast cancer cells by immunohistochemistry in patients' material. Moreover, we demonstrated high expression and constitutive secretion of serglycin in the aggressive MDA-MB-231 breast cancer cell line. Serglycin exhibited a strong cytoplasmic staining in these cells, observable at the cell periphery in a thread of filaments near the cell membrane, but also in filopodia-like structures. Serglycin was associated with intracellular proteins involved in cytoskeleton formation and mRNA maturation and translation. Serglycin was purified from conditioned medium of MDA-MB-231 cells, and represented the major proteoglycan secreted by these cells, Serglycin carried chondroitin sulfate side chains, mainly composed of 4-sulfated disaccharides. Stable expression of serglycin in less aggressive MCF-7 breast cancer cells induced their proliferation, anchorage-independent growth, migration and invasion through activation of chemokine signaling pathways. Interestingly, over-expression of serglycin lacking the glycosaminoglycan attachment sites failed to promote these cellular functions, suggesting that glycanation of serglycin is a pre-requisite for its oncogenic properties. Serglycin over-expression in breast cancer cells induced the biosynthesis of inflammatory mediators such as interleukins and their receptors as well as matrix degrading enzymes. Purified serglycin inhibited early steps of both the classical and the lectin pathways of complement by binding to C1q and mannose-binding lectin. Furthermore, serglycin strongly bound to osteoprotegerin. Serglycin promoted osteoclastogenesis and biosynthesis of bone degrading enzymes since it bound to osteoprotegerin and reduced its ability to block the action of RANKL in relation to differentiation of osteoclasts.

Our findings suggest that serglycin promotes a more aggressive breast cancer cell phenotype and augments breast cancer-induced bone destruction. Furthermore, it may also protect breast cancer cells from complement system attack supporting their survival and expansion.