Short Communication Journal of Molecular and Cellular Biochemistry 2020
Vol.4 No.2

Glycobiology 2020: The heparan sulfate proteoglycan Syndecan-1 and heparanase are novel regulators of cancer stem cell function and therapeutic resistance - Martin Gotte- Munster University Hospital

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Introduction:

The heparan sulfate proteoglycan Syndecan-1 binds cytokines, morphogens and extracellular matrix components, regulating cancer stem cell properties and invasiveness. Syndecan-1 is modulated by the heparan sulfate-degrading enzyme heparanase, but the underlying regulatory mechanisms are only poorly understood (1). In colon cancer pathogenesis, complex changes occur in the expression pattern of Syndecan-1 and heparanase during progression from well-differentiated to undifferentiated tumors. Loss of Syndecan-1 and increased expression of heparanase are associated with a change in phenotypic plasticity and an increase in invasiveness, metastasis and dedifferentiation. Here we investigated the regulatory and functional interplay of Syndecan-1 and heparanase employing siRNA-mediated silencing and plasmid-based overexpression approaches in human colon cancer cell lines and in a xenograft model . Sdc-1 small-interfering RNA knockdown in the human colon cancer cell lines Caco2 and HT-29 resulted in an increased side population (SP), enhanced aldehyde dehydrogenase 1 activity, and higher expression of CD133, LGR5, EPCAM, NANOG, SRY (sex-determining region Y)-box 2, KLF2, and TCF4/TCF7L2. Notably, heparanase expression and activity were upregulated in Syndecan-1 depleted cells. This increase was linked to an upregulation of the transcription factor Egr1, which regulates heparanase at the promoter level. Sdc-1 knockdown enhanced sphere formation, cell viability, Matrigel invasiveness, and epithelial-to-mesenchymal transition-related gene expression. Likewise, upregulation of heparanase increased the colon cancer stem cell phenotype based on sphere formation assays and phenotypic marker analysis (Side-population, NANOG, KLF4, NOTCH, Wnt, and TCF4 expression). Sdc-1-depleted HT-29 xenograft growth was increased compared to controls. Decreased Sdc-1 expression was associated with an increased activation of β1-integrins, focal adhesion kinase (FAK), and wingless-type (Wnt) signaling. Pharmacological FAK, Wnt and heparanase inhibition blocked the enhanced stem cell phenotype and invasive growth. Sequential flow cytometric SP enrichment substantially enhanced the stem cell phenotype of Sdc-1-depleted cells, which showed increased resistance to doxorubicin chemotherapy and irradiation. In addition, upregulated expression of heparanase resulted in increased resistance to radiotherapy, whereas high expression of enzymatically inactive heparanase promoted chemoresistance to paclitaxel and cisplatin. In conclusion, Sdc-1 depletion cooperatively enhances expression of heparanase and activation of integrins and FAK, which then generates signals for increased invasiveness and cancer stem cell properties. Our findings provide a new avenue to target a stemness-associated signaling axis as a therapeutic strategy to reduce metastatic spread and cancer recurrence.

Results and Discussion: In colon cancer, downregulation of the transmembrane heparan sulfate proteoglycan syndecan-1 (Sdc-1) is associated with increased invasiveness, metastasis, and dedifferentiation. As Sdc-1 modulates signaling pathways relevant to stem cell function, we tested the hypothesis that it may regulate a tumor-initiating cell phenotype. Sdc-1 small-interfering RNA knockdown in the human colon cancer cell lines Caco2 and HT-29 resulted in an increased side population (SP), enhanced aldehyde dehydrogenase 1 activity, and higher expression of CD133, LGR5, EPCAM, NANOG, SRY (sex-determining region Y)-box 2, KLF2, and TCF4/TCF7L2. Sdc-1 knockdown enhanced sphere formation, cell viability, Matrigel invasiveness, and epithelial-to-mesenchymal transition-related gene expression. Sdc-1-depleted HT-29 xenograft growth was increased compared to controls. Decreased Sdc-1 expression was associated with an increased activation of β1-integrins, focal adhesion kinase (FAK), and wingless-type (Wnt) signaling. Pharmacological FAK and Wnt inhibition blocked the enhanced stem cell phenotype and invasive growth. Sequential flow cytometric SP enrichment substantially enhanced the stem cell phenotype of Sdc-1-depleted cells, which showed increased resistance to doxorubicin chemotherapy and irradiation. In conclusion, Sdc-1 depletion cooperatively enhances activation of integrins and FAK, which then generates signals for increased invasiveness and cancer stem cell properties. Our findings may provide a novel concept to target a stemness-associated signaling axis as a therapeutic strategy to reduce metastatic spread and cancer recurrence. DATABASES: The GEO accession number of the Affymetrix transcriptomic screening is GSE58751

This work is partly presented at 10th Glycobiology World Congress webinar July on 17-18, 2020