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Sommario/riassunto	In recent decades, evidence has accumulated implicating heparan sulfate proteoglycans (HSPGs) in tumor initiation and progression. Ubiquitously present at the cell surface and in the extracellular matrix, HSPGs are composed of a protein core with covalently bound heparan sulfate (HS) chains. They present high structural complexity and heterogeneity provided by the coordinated action of several biosynthetic and HS modifying enzymes in a tissue - and cell type-specific manner. The absence of HS is incompatible with life, highlighting the critical role of HS and HSPGs in key physiological processes including cell adhesion, migration, invasion as well as cell signaling. The essential contribution of HSPGs to these processes depends on the ability of HS to bind hundreds of proteins and to modulate their activity. This unique property allows HSPGs to exert multiple functions either structural, by conferring integrity and insolubility to the extracellular matrix, or functional, by regulating bioavailability and signaling of growth factors and cytokines. Shedding of the core protein by proteases and degradation of HS by the endoglycosidase heparanase, which produce bioactive molecules, further extends and adds complexity to the biological functions of HSPGs. Altered expression or deregulated function of HSPGs, or of their biosynthetic/modifying enzymes, has been reported in several tumor

types and a vast literature supports their participation in inflammation, tumor growth, angiogenesis and metastasis. Moreover, heparanase and enzymes that edit regulate the sulfation pattern of HS, endosulfatases and sulfotransferases, have emerged as players able to influence the response of tumors to therapy. HSPGs and HS modifying enzymes have attracted much interest as potential biomarkers and antitumor therapeutic targets, supported by promising preclinical studies. Several biological and pharmacological targeting approaches are under intensive investigation. Currently, however, only a few early clinical trials include HS mimetics or heparanase inhibitors, HSPG-directed monoclonal antibody and peptide vaccine, or are testing HSPGs as a candidate tumor biomarker. A deeper insight into the roles of HSPGs and related enzymes in the pathogenesis and progression of specific tumor types and sub-types is expected to favor the transilation of preclinical studies to the clinic. In this Research Topic, we collect articles highlighting the pathological role of HSPGs and HS modifying enzymes in specific tumor contexts, elucidating their pleiotropic effects and investigating their biomarker and target significance, with the aim of fully exploiting their potential value in diagnosis, prognosis and treatment using novel therapeutic approaches.