ANGIOGENESIS AND INFLAMMATION: THE VICIOUS CIRCLE OF PGE2 AND TYROSINE KINASE RECEPTORS

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The composition of the interstitial fluid has been reported to influence both tumor growth and new vessel formation. Recently, we focused on prostaglandin E2 (PGE2) trying to define its role in controlling tumor progression and angiogenesis. PGE2 contributes to carcinogenesis through the activation of EP receptors and through the cross-talk with growth factors via their tyrosine kinase receptors. Recently, we demonstrated that PGE2 induces epidermal growth factor receptor (EGFR) transactivation in squamous cell carcinoma, promoting tumor cell growth and invasiveness (1). In this tumor the nitric oxide synthase/guanylate cyclase (NOS/GC) pathway, crucial in mediating angiogenesis, is the required step for PGE2 effects. PGE2 activities, confined to the selective stimulation of the EP2 receptor subtype, lead to EGFR transactivation via protein kinase A (PKA) and c-Src. In these studies, the iNOS/GC signalling emerged as a downstream player in the control of EP2/EGFR-mediated tumor cell proliferation and invasion. Complementing its tumor promoting activity, PGE2 promotes angiogenesis (2). We investigated the PGE2 activity on microvascular endothelial cells with the purpose of delineating the signalling pathway leading to new vessels formation. In endothelial cells PGE2 activates a paracrine-exocrine mechanism (vicious circle) which operates to maintain cell viability. Infact, PGE2 exerts chemotactic activity on endothelium through the rapid activation and phosphorylation of the tyrosine kinase receptor for the fibroblast growth factor-2 (FGFR-1). FGFR-1, when activated, serves as a general cell transcription regulator, promoting the expression/production of its ligand, FGF-2. These data highlight the relevance of the inflammatory mediators as a “fuel” for both tumor growth and angiogenesis. The specific interaction between EPs and tyrosine kinase receptors stands as an amplifying circuit to be considered in therapies employing tyrosine kinase receptor inhibitors as antitumor/antiangiogenic drugs.

References

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