Interaction between mPGES-1 and iNOS in the activation of stem-like phenotype in EGFR-driven epithelial tumor cells

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Inflammatory prostaglandin E-2 (PGE-2) favors cancer progression in epithelial tumors characterized by persistent oncogene input. However, its effects on tumor cell stemness are poorly understood at molecular level. Here we describe two epithelial tumor cells A431 and A459, originating from human lung and skin tumors, in which epithelial growth factor (EGF) induces sequential up-regulation of mPGES-1 and iNOS enzymes, producing an inflammatory intracellular milieu. We demonstrated that concerted action of EGF, mPGES-1 and iNOS causes sharp changes in cell phenotype demonstrated by acquisition of stem-cell features and activation of the epithelial-mesenchymal transition (EMT). When primed with EGF, epithelial tumor cells transfected with mPGES-1 or iNOS to ensure steady enzyme levels display major stem-like and EMT markers, such as reduction in E-cadherin with a concomitant rise in vimentin, ALDH-1 and CD133. Tumorsphere studies with these cells show increased sphere number and size, enhanced migratory and clonogenic capacity and sharp changes in EMT markers, indicating activation of this process. The concerted action of the enzymes forms a well-orchestrated cascade where expression of iNOS depends on overexpression of mPGES-1. Indeed, we show that through its downstream effectors (PGE-2, PKA, PI3K/Akt), mPGES-1 recruits non-canonical transcription factors, thus facilitating iNOS production.

In conclusion, we propose that the initial event leading to tumor stem-cell activation may be a leveraged intrinsic mechanism in which all players are either inherent constituents (EGF) or highly inducible proteins (mPGES-1, iNOS) of tumor cells. We suggest that incipient tumor aggressiveness may be moderated by reducing pivotal input of mPGES-1.