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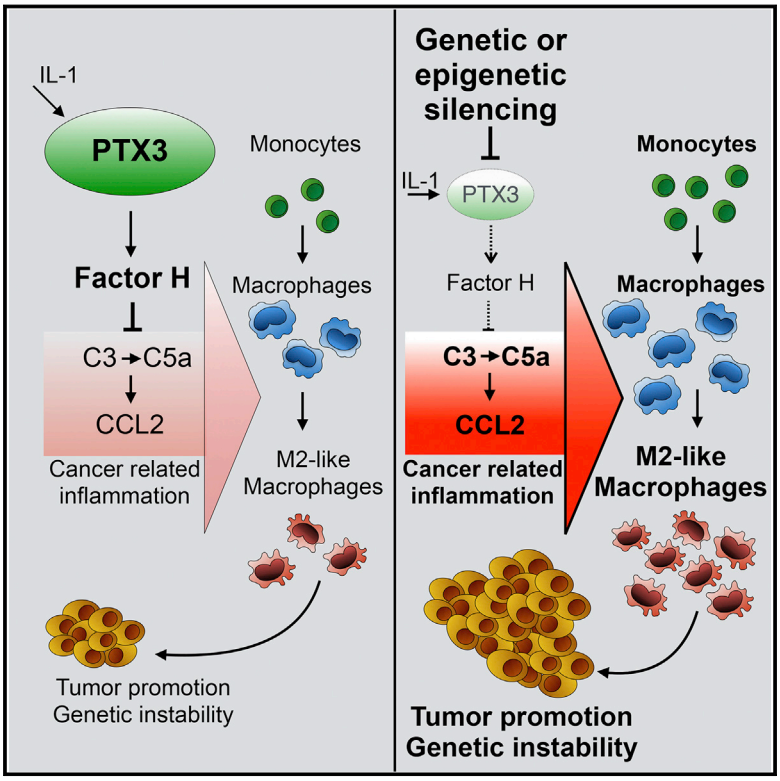
PTX3 Is an Extrinsic Oncosuppressor Regulating Complement-Dependent Inflammation in Cancer

Graphical Abstract



Highlights

- PTX3 deficiency unleashes Complement-dependent tumor-promoting inflammation
- Tumors developed in a PTX3-deficient context have higher frequency of mutated *Trp53*
- PTX3 expression is epigenetically repressed in selected human tumors
- Complement is an essential component of tumor-promoting inflammation

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In Brief

PTX3 deficiency triggers Complement-dependent tumor-promoting inflammation, with enhanced tumor burden, macrophage infiltration, cytokine production, angiogenesis, and genetic instability, revealing the role of this innate immunity mediator as an extrinsic oncosuppressor.

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PTX3 Is an Extrinsic Oncosuppressor Regulating Complement-Dependent Inflammation in Cancer

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SUMMARY

PTX3 is an essential component of the humoral arm of innate immunity, playing a nonredundant role in resistance against selected microbes and in the regulation of inflammation. PTX3 activates and regulates the Complement cascade by interacting with C1q and with Factor H. PTX3 deficiency was associated with increased susceptibility to mesenchymal and epithelial carcinogenesis. Increased susceptibility of *Ptx3*$^{-/-}$ mice was associated with enhanced macrophage infiltration, cytokine production, angiogenesis, and *Trp53* mutations. Correlative evidence, gene-targeted mice, and pharmacological blocking experiments indicated that PTX3 deficiency resulted in amplification of Complement activation, CCL2 production, and tumor-promoting macrophage recruitment. PTX3 expression was epigenetically regulated in selected human tumors (e.g., leiomyosarcomas and colorectal cancer) by methylation of the promoter region and of a putative enhancer. Thus, PTX3, an effector molecule belonging to the humoral arm of innate immunity, acts as an extrinsic oncosuppressor gene in mouse and man by regulating Complement-dependent, macrophage-sustained, tumor-promoting inflammation.