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Role of PTX3 and complement modulation in the tumor microenvironment

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Abstract: Pentraxin-3 (PTX3), the prototype of long pentraxins, seems to influence complement system (CS) modulation. PTX3 and CS sustain carcinogenesis, enriching tumor microenvironment (TME) with pro-inflammatory molecules promoting angiogenesis in prostate cancer (PC) and renal cell carcinoma (RCC). Furthermore, cancer cells overexpress complement regulatory proteins, such as CD46, CD55 and CD59, which negatively affect complement pathways for support cancer cells survival. This viewpoint aims to elucidate the ambivalent role of PTX3 and the CS in the context of tumor microenvironment (TME).

Introduction

Pentraxins, a superfamily of evolutionary conserved proteins, are essential components of innate immune system and play a pivotal role in vascular biology (Garlanda *et al.*, 2005; Peri *et al.*, 2000). Pentraxin-3 (PTX3), the prototype of long pentraxins, differs from short pentraxins for gene organization, cellular source, and ligand-binding capacities (Peri *et al.*, 2000; Mantovani *et al.*, 2006). Like short pentraxins, PTX3 facilitates dysregulation of mitogenic signaling pathways, sustains cellular proliferation, angiogenesis, metastasis formation, insensitivity to apoptosis, and tumor escape from immunosurveillance (Baruah *et al.*, 2006; Rutkowski *et al.*, 2010). Unlike short pentraxins, PTX3 is synthesized by a variety of cell types at the site of inflammation (Garlanda *et al.*, 2005; Schenk *et al.*, 2010), whereby it seems to regulate complement system (CS) activation (Garlanda *et al.*, 2005; Rutkowski *et al.*, 2010). Recent findings suggest an insidious relationship between complement and cancer in terms of cellular proliferation and regeneration as well as angiogenesis (Rutkowski *et al.*, 2010; Diamandis *et al.*, 2011).

This viewpoint aims to elucidate the mechanisms responsible for tumor progression focusing on the ambivalent role of PTX3 and the CS in the context of tumor microenvironment (TME).

Presentation

Recently, new investigations in the field of TME highlighted that switching from acute to chronic immunoflogosis continuously provides the tumor with a cytokines-rich milieu therefore promoting cancer survival (Korniluk *et al.*, 2017). Of note, PTX3 has emerged as an ambivalent inflammatory mediator acting as a tumor suppressor and pro-oncogenic factor depending on the TME in which it is found (Ronca *et al.*, 2013; Giacomini *et al.*, 2018) (Fig. 1). PTX3 may modulate the CS by binding to C1q and MBL, thus activating the classical and the lectin pathway, and to CFH, thus affecting the alternative pathway (Ma and Garred, 2018). CS activation leads to the C3 cleavage and C5b-9 complex assembly to direct lyse the pathogens and cell debris empowering the inflammation both at the systemic and locally level.

In the tumour milieu complement mediators both induce an anti-tumour response mainly via their lytic activity by enriching the TME with immunosuppressive factors and promote carcinogenesis by releasing very strong pro-inflammatory molecules, such as the anaphylatoxins C3a and C5a therefore sustaining neoangiogenesis and metastasis

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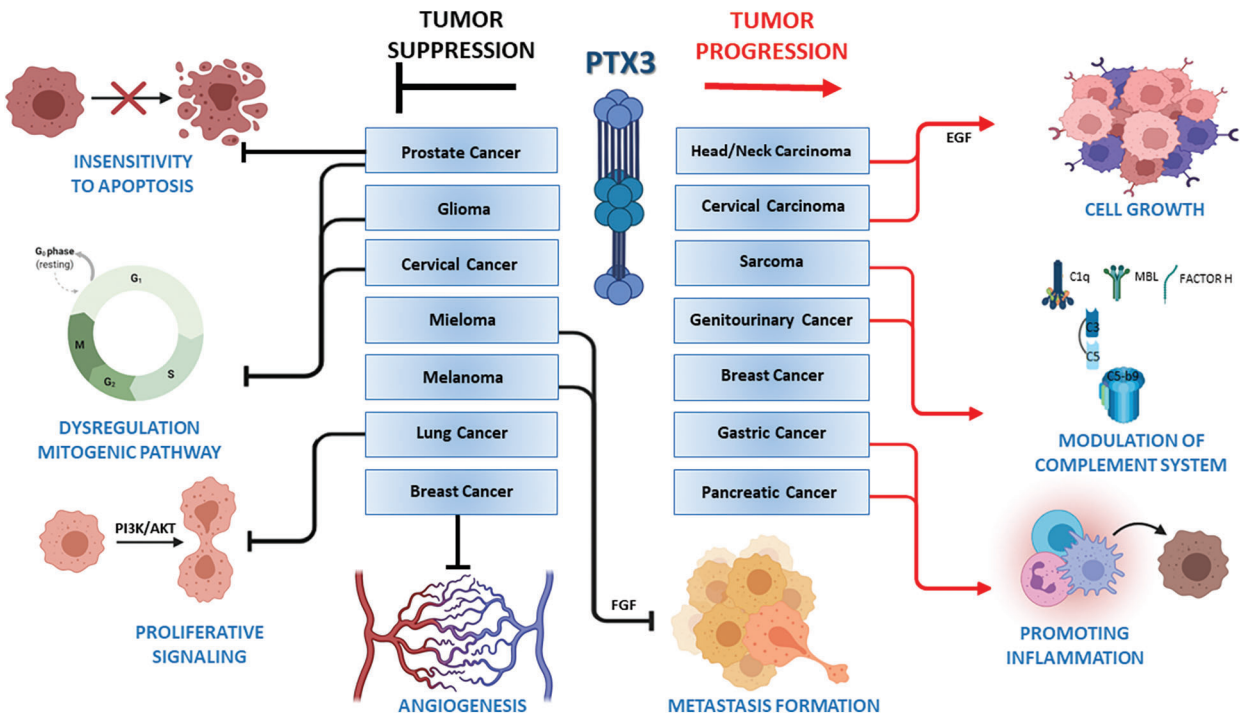

FIGURE 1. The ambivalent role of PTX3 in cancers. The role of PTX3 in cancer pathogenesis is likely to be context and pathway dependent. PTX3 may act as a tumor suppressor factor by inducing insensitivity to apoptosis or cell-cycle arrest in Glioma, Prostate and Cervical Cancer. Of note, PTX3 may binds to members of fibroblast growth factor family (FGF), including FGF2, and FGF8b by inhibiting FGF-dependent metastasis formation in Mieloma and Melanoma. A modulation in proliferative signaling, involving the most frequently over-activated intracellular pathways PI3K/AKT was reported for lung cancer as well as a decreased tendency to sustain neoangiogenesis for breast cancer. On the contrary, PTX3 seems to act as pro-tumorigenic factor in head/neck carcinoma and cervical carcinoma by acting on epidermal growth factor (EGF) to support neoplastic proliferation. The ability to modulate the complement system leads PTX3 to induce neoangiogenesis and cancer development via the release of the anaphylatoxins in the absence of cell-lysis damage on neoplastic cells in the context of prostate and renal cancer. Of note, the lack of recruitment of FH due to PTX3 deficiency promote carcinogenesis in sarcoma. In addition, an increase of PTX3-mediated inflammation has been reported for gastric and pancreatic cancer.

formation (Rutkowski *et al.*, 2010). Of note, also PTX3/CFH balance may modulate CS activation as well as CFH different expression may affect cancer development (Bonavita *et al.*, 2015; Daugan *et al.*, 2021b; Riihilä *et al.*, 2019). In the attempt to avoid C5b-9-mediated lysis and to allow cell survival, cancer cells may modulate and/or remove C5b-9 complex by upregulating the membrane bound Complement Regulatory Proteins (mCRPs), including CD55, CD59, CD46 (Gigante *et al.*, 2013; Santangelo *et al.*, 2014; Pio *et al.*, 2014; Castellano *et al.*, 2019; Geller and Yan, 2019) (Fig. 2).

The role of CS in sustain carcinogenesis is particularly relevant in the context of genitourinary cancers. As known, patients affected by prostate cancer (PC) show increased level of prostate-specific antigen (PSA), a serine protease that among others is able to cleave C3 and C5 *in vitro*, acting as complement activating-protease (Manning *et al.*, 2013). In accordance, elevated level of C3 fragments were found in the serum of PC patients (Manning *et al.*, 2013; Karczmarski *et al.*, 2013) and an increased expression of CD55 and CD59 were observed in patients with advanced PC and decreased overall survival (OS) (Loberg *et al.*, 2006; Xu *et al.*, 2005).

The ability of CS in promoting cancer progression by activating angiogenesis is amplified in renal cell carcinoma (RCC) since renal cells may produce all complement effectors mainly triggering the classical pathway (Reese *et al.*, 2020; Tang *et al.*, 1999, Daugan *et al.*, 2021a; Roumenina *et al.*, 2019). The finding of elevated C5a level in ccRCC patients resulted as an adverse prognostic feature (Zhou *et al.*, 2001) related to C5a-mediated immunosurveillance evasion (Corrales *et al.*, 2012; Hezmee *et al.*, 2011). As regard mCRPs, an increased expression of CD55/CD59 and CD46 were correlated to ccRCC progression and tumor stage, respectively (Blok *et al.*, 2000).

Noteworthy, PC and RCC patients showed an increased tissue and serum expression of PTX3, as compared to non-neoplastic patients. Looking into PC patients, elevated PTX3 serum levels were also able to discriminate PC from prostatic inflammation and benign prostatic hyperplasia (BPH) (Stallone *et al.*, 2014; Falagario *et al.*, 2021). Recent studies reported that PTX3 is able to modulate CS in PC and RCC TME since it co-localizes with C1q deposits, CD59 and with C3a-C5a receptors in PC biopsies and RCC tissues (Stallone *et al.*, 2020; Netti *et al.*, 2020). Interestingly, these studies showed no evidence of PTX3 and C5b-9 co-localization in both cancers, thus reinforcing the hypothesis of pro-tumorigenic effect of both CS and PTX3 in sustaining neoangiogenesis in the absence of cell-lysis damage on neoplastic cells.

Conclusion and Future Perspectives

Inflammation and CS have emerged as a double-edged sword acting as tumor-suppressor by generating an immunosuppressive TME or as pro-oncogenic factor promoting cancer development.

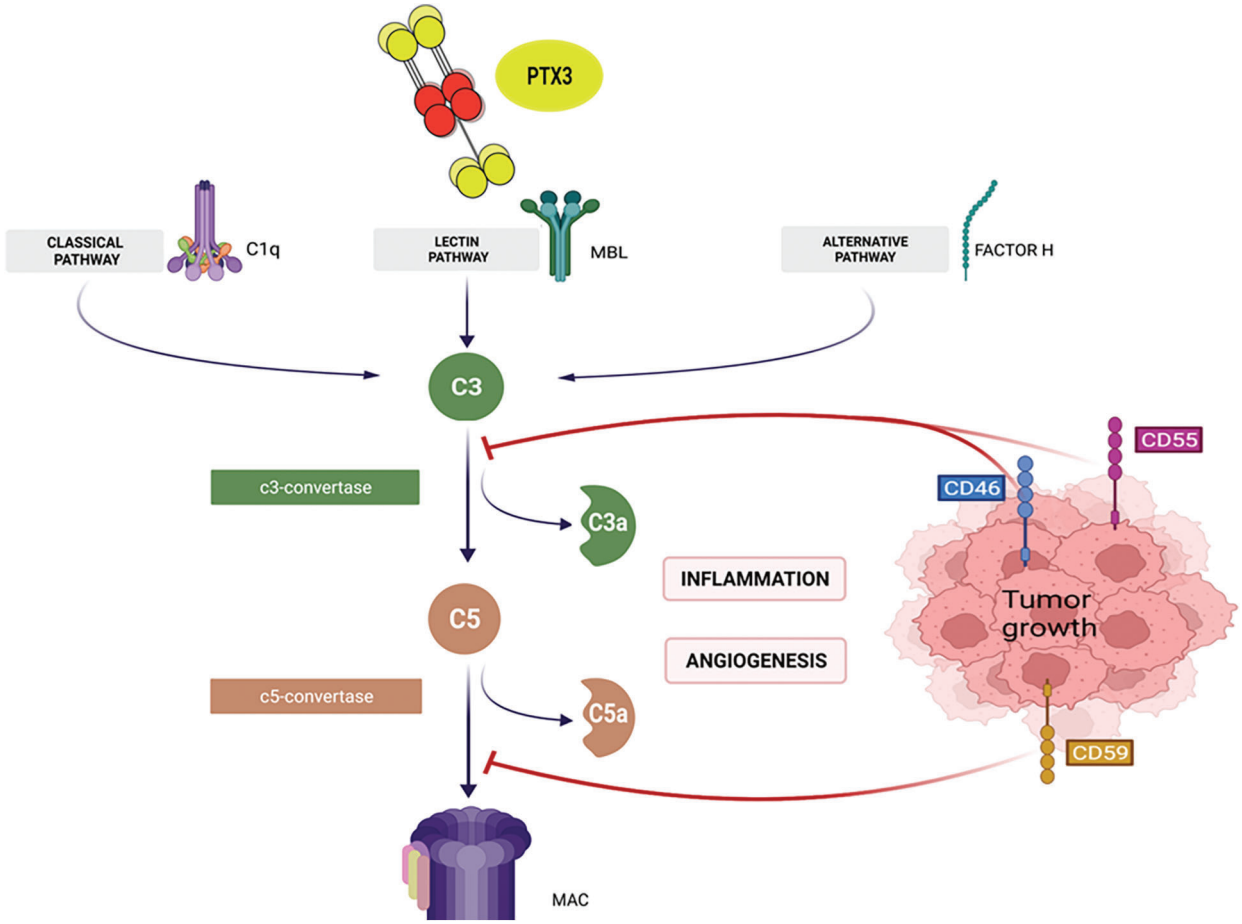

FIGURE 2. Involvement of PTX3 in complement system modulation in cancer. PTX3 is involved in Complement System (CS) activation and regulation by interacting with complement components, influencing inflammation and neoplastic angiogenesis. (A, B) PTX3 can binds to C1q and mannose-binding lectin (MBL) and activate classical pathway and lectin pathway, respectively or (C) can interact with complement regulators, such as Factor H, affecting the alternative pathway. As a consequence of CS activation, the cleavage of C3 and of C5 leads to the deposition of C3a and C5a anaphylotoxins, which sustain inflammation and neoangiogenesis, enhancing tumor growth. In addition, cancer cells overexpress different Membrane bound Complement Regulatory Proteins (mCRPs), including membrane cofactor protein (CD46), decay-accelerating factor (CD55) and protectin (CD59) which inhibit the formation of MAC and cell lysis, supporting cancer cells survival.

PTX3 and CS are crucial and ambivalent mediator in PC and RCC. Taken together, these findings suggest a possible key role of PTX3 and CS for cancer progression in the context of TME.

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