NF-κB Pathway in Pancreatic Cancer

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Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal cancers with no effective treatment option. A predominant hallmark of PDAC is the intense fibro-inflammatory stroma which not only physically collapses vasculature but also functionally suppresses anti-tumor immunity. Constitutive and induced activation of the NF-κB transcription factors in neoplastic cells, stromal fibroblasts, and immune cells is a major mechanism that drives inflammation in PDAC. While targeting this pathway is widely supported as a promising therapeutic strategy, clinical success is elusive due to a lack of safe and effective anti-NF-κB pathway therapeutics.

Keywords: NF-KB, ; pancreatic cancer, ; inflammation, ; IRAK4, ; TPL2 , ; TAK1

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) has recently emerged as the third leading cause of cancer-related death in the US and is projected to be the second by 2030 [1]. Due to a lack of early symptoms and effective screening strategies, only 10–15% of PDAC patients are diagnosed at an early stage that allows surgical resection. For these patients, adjuvant chemotherapies are routinely offered [2][3][4]. Yet, the majority of these patients succumb to disease relapse, indicating the strong resistance of PDAC cells to chemotherapy. For patients with inoperable or metastatic diseases, combination chemotherapies including FOLFIRINOX (cocktail of 5-FU, oxaliplatin, leucovorin and irinotecan) and gemcitabine/nab-paclitaxel are the mainstay treatment [5][6], but treatment response is neither universal nor durable. This dire scenario translates into an estimated 47,050 deaths, or ~82% of new 57,600 PDAC cases diagnosed in the US in 2020 [7]. The 5-year survival rate for all PDAC patients is currently at ~9%, the lowest among all major cancer types. Despite decades of intensive research from the academia and industry, newer treatment modalities including molecular-targeted and immunotherapies, which are part of standard treatments for other cancer types, remain largely unsuccessful in PDAC.

Several factors, both intrinsic and extrinsic, contribute to the aggressive behavior of PDAC. PDAC cells are intrinsically driven by powerful oncogenic mutations, including activating KRAS mutations, loss of TP53, and CDKN2A/B and SMAD4 tumor suppressor genes [8], which endow PDAC cells with superior capabilities to survive in adverse environments, withstand therapeutic attacks, and metastasize. Externally, the tumor microenvironment (TME) of PDAC is characterized by a thick, densely fibrotic (desmoplastic) matrix consisting of collagen, hyaluronan, and fibronectin, which can constitute up to 80–90% of the tumor bulk [9]. Studies over the past two decades have shown that the desmoplastic stroma not only limits vascularity and delivery of therapeutics but is also heavily infiltrated with suppressive immune cells that incapacitate anti-tumor T cells [10][11][12][13]. However, addition of stroma-depleting agents, especially sonic Hedgehog inhibitors or pegylated hyaluronidase, to chemotherapy failed to benefit patients in clinical trials [14][15][16][17]. Furthermore, mouse models suggest that depletion of stromal fibroblasts alone carries a risk of reverting PDAC cells to a progenitor-like and aggressive state that is more treatment-resistant [13][18]. Therefore, an in-depth understanding of the tumor-intrinsic and -extrinsic signaling pathways that contribute to desmoplasia is essential in devising effective therapeutic strategies.

2. NF-κB Pathway: A Major Driver of Inflammation in PDAC

Aberrant activation of the NF-κB family of transcription factors is perhaps the most common and dominant mechanism that drives chronic inflammation in human cancers. The NF-κB factors comprise of five different members: RELA (p65), RELB, c-REL, p50/p105, and p52/100 [19]. They are classified as NF-κB/Rel proteins as they all share a Rel homology domain (RHD) in the N-terminus, which is critical for homo- or hetero-dimerization and binding to κB cognate DNA elements in target genes. The activity of NF-κB is principally regulated by inhibitors of κB (IκBs) which mask the nuclear localization signals (NLS) of NF-κB, keeping them sequestered in an inactive latent complex in the cytoplasm [20]. There are canonical and non-canonical NF-κB pathways. In the canonical pathway, the IκB kinases (IKK) phosphorylate IκB upon receiving extracellular signals, such as cytokines, stress, free radicals, or radiation, resulting in the polyubiquitination and proteasomal degradation of IκB. This leads to the release of p65 and p50 which can translocate into the nucleus to

transactivate κB-dependent genes [21]. The non-canonical pathway involves p100/RelB complexes which, at baseline, are inactive in the cytoplasm. Signaling through receptors, such as CD40 and the lymphotoxin β receptor (LTβR), activates the NF-κB-inducing kinase (NIK), which in turn activates IKKα, leading to phosphorylation of p100 at the C-terminal residues. This results in polyubiquitination and proteasomal processing of p100 to p52 which can translocate into the nucleus and complex with RELB to transactivate target genes [22]. In PDAC, the canonical pathway is the main driving mechanism of NF-κB activity.

2.1. The Role of NF-κB in PDAC Cells

Constitutive activation of NF-κB occurs in ~70% of PDAC samples [23][24], as seen by increased immunohistochemical staining of phosphorylated or nuclear RELA in neoplastic cells. Apart from inflammation, the NF-κB transcription factors control genes that contribute to various hallmarks of cancer, which include proliferation, evasion from apoptosis, enhanced angiogenesis, metastasis, and invasion [21][25][26]. Several review articles have been published delineating the pro-tumorigenic roles of NF-κB in PDAC, and these will not be described in detail here. Importantly, NF-κB activity can be further induced under stress conditions, including DNA damage, and is a major mechanism that confers resistance to chemotherapeutic agents, such as gemcitabine [27][28][29][30]. Mechanistically, NF-κB activation slows down the cell-cycle, thereby desensitizing PDAC cells to chemotherapy, inducing anti-apoptotic proteins that block the caspase activation, and inducing stemness [31][32].

2.2. The Role of NF-κB in CAFs

Cancer-associated fibroblasts (CAFs) play a major role in treatment resistance and progression of PDAC [33][34]. However, near depletion of CAFs paradoxically promotes the development of more aggressive and poorly differentiated PDAC [13][18]. It is now clear that PDAC CAFs consist of at least three different transcriptomic subtypes: inflammatory CAFs (iCAFs), myofibroblastic CAFs (myCAFs), and antigen-presenting CAFs (apCAFs) [35][36]. Robust phosphorylation of RELA was observed in a subset of PDAC CAFs and is critical for collagen deposition and secretion of inflammatory cytokines, including IL-6 and IL-1β [37], suggesting NF-κB to be the driving force in iCAFs. Importantly, the abundance of IL-1β staining in CAFs is associated with poor prognosis. Mechanistically, RELA activation in CAFs is driven by IL-1β secreted from CAFs, and surrounding PDAC cells and can be blocked by interleukin-1 receptor-associated kinase (IRAK)4 inhibition. PDAC cells injected into IRAK4-null mice or co-injected with IRAK4-silenced CAFs develop markedly smaller and less fibrotic tumors [37]. Notably, IRAK4 inhibitors markedly reduce tumor fibrosis and synergize with gemcitabine, leading to significantly better tumor control. These results provide a tractable strategy to selectively target iCAFs to improve therapeutic response. In addition, recent evidence has shown that pancreatic stellate cells (PSCs) secrete chemokine (C-X-C motif) ligand 2 (CXCL2) by engaging p50 to block $CD8^+$ T cell infiltration in PDAC [38]. This further supports the rationale to target the NF-κB cascade in CAFs.

2.3. The Role of NF-κB in Immune Cells

The role of NF-κB factors in immune cells is extremely complicated, context dependent, and mostly studied using conditional knockout mouse models. The role of NF-κB in each immune subset in PDAC is largely unclear. In PDAC, certain subsets of myeloid-derived suppressor cells (MDSCs) and tolerogenic regulatory T (Treg) cells actively contribute to tumor progression and treatment resistance [39][40]. Granulocytic MDSCs (G-MDSCs) constitute 70–80%, or higher, whereas mononuclear MDSCs (M-MDSCs) constitute 20–30% of the total population of MDSCs. On the other hand, anti-tumor $CD4^+$ and $CD8^+$ T cells are either scarce or dysfunctional. The crosstalk of MDSCs with immune cells, such as tumor associated macrophages (TAMs), Tregs, and dendritic cells (DCs), within the tumor microenvironment (TME)suppresses effector T cells. The role of NF-κB in driving the phenotypes of these immune cells and the impact of targeting the canonical or non-canonical NF-κB pathways in PDAC is largely unclear and should be investigated. Until then, it is important to appreciate the role of the NF-κB pathway in the development of each immune cell type. Both the canonical and non-canonical pathways are essential for normal differentiation and self-renewal of hematopoietic stem cells [41][42]. Vav-Cre driven deletion of RELA, which ablates RELA expression in all hematopoietic cells, resulted in accumulation of hematopoietic stem cells that are defective in further differentiation into progenitors [41]. Interestingly, myeloid-specific deletion or pharmacologic suppression of IKKβ resulted in granulocytosis and rendered mice more susceptible to endotoxin-induced shock due to increased circulating IL-1β and TNFα [43]. On the other hand, bone marrow transplant experiments showed that IKKβ-deleted stem cells failed to mature into T cells due to overwhelming TNFα-induced apoptosis, and this defect could be fixed/prevented by co-deletion of TNF receptor (TNFR) [44]. Tightly regulated canonical NF-κB activity is essential for positive and negative selection of major histocompatibility complex (MHC)-1 restricted $CD8^+$ T cell selection, as these processes are abrogated by excessive or inadequate canonical NF-κB activity mimicked by expression of activated IKKβ mutant or dominant negative IκB in T cells [45]. Intriguingly, these mutant T cells retained a normal ability to undergo MHC-II restricted $CD4^+$ T cell selection, suggesting that the canonical NF-κB activity

is dispensable in $CD4^+$ T cell selection [45]. That said, RELA is critical for maintenance of tolerogenic $CD4^+$ $Foxp3^+$ Treg as deletion of RELA in this subset induces autoimmune disorders [46]. The activation of NF-kB downstream of MyD88 has a critical role in the activation and functionality of MDSCs. The ability of $MyD88^{-/-}$ MDSCs to suppress the activity of T cells and secrete immunoregulatory cytokines was considerably reduced compared to the wild-type MDSCs both in vitro and in vivo. Also, the activation of NF-κB signaling in TAMs contributes to carcinogenesis in various models of inflammation-associated cancers including PDAC [47]. In B cells, IKKβ is essential for survival, proliferation, maturation, and mounting antibody response to T cell dependent and independent antigens [48][49][50].

To date, immunotherapy, specifically "immune checkpoint inhibitors" (ICIs) and chimeric antigen receptor (CAR) T cells, remains largely unsuccessful in PDAC. Attempts to relieve T cell checkpoints with anti- (programmed death) PD-1/anti-PD- ligand(L)1 and/or anti- cytotoxic T-lymphocyte-associated protein 4 (CTLA4) are inadequate in mounting an effective therapeutic response. One of the major obstacles is T cell exhaustion, which is driven by upregulation of the transcription factors nuclear factor of activated T cells (NFAT), basic leucine zipper ATF-like transcription factor (BATF), and interferon regulatory factor 4 (IRF4) [51][52][53]. However, the molecular mechanisms that upregulate these factors remain largely unclear. Chronic engagement of the Toll-like receptor (TLR)7 or infection with HIV leads to anergy of $CD4^+$ T cells via NFAT cytoplasmic 2 (NFATc2) [54]. Sustained engagement of T cell receptors or TLR engagement, as expected within the inflammatory TME of PDAC, may contribute to the upregulation of these exhaustion factors, but this speculation remains to be tested.

3. Therapeutic Targeting of the NF-κB Pathway in PDAC

Several hundreds of agents have been proposed to have anti-NF-κB activities [55]. On the one hand, this scenario highlights the importance of this pathway in cancer therapy. On the other hand, it accentuates the lack of specific inhibitors that can effectively and safely curb this pathway in the clinic. Small peptides or peptidomimetics that directly interfere with NF-κB dimerization or binding with DNA have been published in preclinical settings [56][57][58], but these have not been advanced into clinical trials. Therefore, much attention is paid towards targeting the signaling nodes, especially kinases, that activate NF-κB. In solid malignancies, including PDAC, the canonical pathway is the predominant mechanism that drives NF-κB and is triggered by inflammatory cytokines [19].

Despite the plethora of preclinical studies employing various “NF-κB targeting” agents, only a few of these candidates have actually entered and completed early phase clinical trials. Although the COX2 inhibitor celecoxib was shown to abrogate NF-κB activity and cooperate with gemcitabine in preclinical studies [59][60], the addition of 400 mg celecoxib twice daily and 81 mg aspirin once daily did not improve the therapeutic efficacy of gemcitabine in a phase II clinical trial [61]. In phase II studies, curcumin given at 8 g/day alone or in combination with gemcitabine showed preliminary biological activity in a few selected PDAC patients [62][63], but it is unclear whether larger clinical trials are being planned. Blocking the degradation of IκB with the proteasome inhibitor bortezomib, which also affects numerous other substrates, did not potentiate gemcitabine in a phase II clinical trial [64]. Despite these setbacks, the recent better understanding of the signaling mechanisms that drive NF-κB activity in PDAC has opened up more opportunities. Targeting IL-1R and IRAK4 is more promising, as active agents are now available or being tested in clinical trials. Recently, dendritic cell vaccination has emerged as a novel strategy to prime host anti-tumor immunity [65]. Specifically, the combination of a dendritic cell vaccine with gemcitabine led to eradication of orthotopic tumors and provided durable protection against PDAC in mouse models [66]. However, whether the NF-κB cascade is involved in antigen presentation by dendritic cells and priming of T cells remains unclear and warrants further investigation. At present, no IKK, TPL2, or TAK1 inhibitors are available for further testing in clinical trials for PDAC.

4. Conclusions and Perspectives

Chronic inflammation, driven by the NF-κB pathway, has a major role in every aspect of PDAC pathobiology, ranging from initiation, progression, and metastasis to treatment resistance. In addition, due to the essential role of this pathway in KRAS-induced PDAC progression, the NF-κB pathway has been, and will undoubtedly remain, an attractive therapeutic target. However, targeting the NF-κB factors and the immediate upstream IKK has been challenging due to the lack of specific and clinically safe therapeutic agents, likely due to the essential role of these targets in normal physiology. With recent understanding of the upstream mechanisms that drive NF-κB in PDAC, novel therapeutic targets have begun to surface. Aside from combination with chemotherapy, targeting the NF-κB pathway as a strategy to potentiate immunotherapy has begun to draw attention. As immunotherapy is not without side effects, it is imperative to gain a deeper and more comprehensive understanding of the role of NF-κB pathway in each cellular compartment, and even in different immune subsets, prior to advancing any therapeutic combinations into clinical trials. In particular, these studies

should be conducted in clinically-relevant settings, such as in GEMMs of humanized mouse models, in which the net impact of systemic NF-κB targeting agents can be assessed. In summary, targeting inflammation through the NF-κB pathway remains a valid direction and warrants more intensive and concerted investigation from the research community.

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