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Review

PKB/Akt-dependent regulation of inflammation in cancer

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ABSTRACT

Chronic inflammation is a major cause of human cancer. Clinical cancer therapies against inflammatory risk factors are strategically determined. To rationally guide a novel drug development, an improved mechanistic understanding on the pathological connection between inflammation and carcinogenesis is essential. PI3K-PKB signaling axis has been extensively studied and shown to be one of the key oncogenic drivers in most types of cancer. Pharmacological inhibition of the components along this signaling axis is of great interest for developing novel therapies. Interestingly, emerging studies have shown a close association between PKB activation and inflammatory activity in the vicinity of the tumor, and either blockade of PKB or attenuation of para-tumoral inflammation reveals a mutual-interactive pattern through pathway crosstalk. In this review, we intend to discuss recent advances of PKB-regulated chronic inflammation and its potential impacts on tumor development.

1. Introduction to inflammation

Inflammation is referred to a series of physiological responses of the organism to a variety of stimuli including pathogens, physical/chemical/radioactive injuries and diseases. Initially it is a physiological, defensive process involving different types of immune and vascular cells to firstly protect tissue from damaging stimuli, and eventually repair the occurred lesion. Inflammation is initiated, amplified and regulated by a multitude of inflammatory factors, which are the critical signaling molecules in the process. They act as baits to activate vascular cells and attract defensive cells to the inflamed areas and to promote wound healing. For example, during the acute phase, it is generally accepted that neutrophils are the major effectors stimulated and first attracted to the injured sites in response to the activation of tissue resident mast cells and macrophages [1], followed by increased recruitment of monocytes and dendritic cells. Migration of such leukocytes is fundamentally mediated through chemotactic cytokines with distinguishable specificities to individual types of leukocytes [2]. Assembly of multiple types of leukocytes at the site of tissue injury is a prerequisite for a successful tissue healing, thus is believed as the most important biological event during acute inflammation.

While inflammation is normally a self limiting process, in some cases it may not terminate properly due to uncoordinated processes between elimination of the noxious or infectious agent and tissue repair. This results in a state of prolonged inflammation, defined as chronic inflammation, potentially leading to progressive tissue damage by excessive secretion of chemokines and sustained activation of a multitude of immune cells. Chronic inflammation is not only due to persistent infection. It can also be caused by a deregulated immune response within initially healthy tissues, resulting in chronic inflammatory and autoimmune diseases such as rheumatoid arthritis, ulcerative colitis, and multiple sclerosis or by other chronic disease conditions such as obesity, which subsequently leads to insulin resistance and diabetes.

It has been appreciated for a long time that prolonged exposure to pro-inflammatory factors as well as products of activated immune cells, in particular radical oxygen species (ROS), during chronic inflammation causes genomic alteration and promotes proliferation that may turn normal cells into cancerous cells [3]. In addition to pathogen infection and autoimmune diseases, many environmental factors such as UV radiation and smoking, can cause chronic inflammation mediated by abnormal activation of a range of protective signaling pathways including oxidative cellular stress. Hyperactivation of these pathways increases genome instability resulting in subsequent high mutation rates, which eventually promotes malignant cellular transformation and uncontrolled cell proliferation. Therefore, inflammation is a powerful biological process with a double-blade sword: on the one side its fine-tuned activity is essential for host defence and repair, while on the other side deregulated, sustained activity is a major causes of a number of diseases including metabolic disorders and cancer.

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2. Molecular pathways linking inflammation and cancer

The connection between cancer and chronic inflammation has been observed in the clinic for decades [4]. Initiating factors of chronic inflammation promoting carcinogenesis include microbial and viral infections (e.g. H. Pylori), chemical (e.g. gastric reflux) and physical stimuli (e.g. smoke), autoimmune diseases and spontaneous local inflammatory events. Cancer-related inflammation often associates with the intra- or para-tumoral infiltration of leukocytes. Well-known examples include bone marrow-derived (BMD) monocytes and tumor-associated macrophages (TAM). In parallel, an enrichment of multiple inflammatory factors including cytokines, chemokines and growth factors characteristically correlate with and support the recruitment and accumulation of different types of immune cells in the tumor microenvironment. Which types of cells express these pro-inflammatory factors and how immune cells are attracted to the tumor microenvironment? Recent efforts have shed some light on the intrinsic signaling pathways linking inflammation and cancer at the molecular level.

Several pathways have been demonstrated to mediate inflammatory response through well-defined pro-inflammatory molecules including cytokines, chemokines, growth factors, matrix proteins and cyclooxygenases/prostaglandins. Cytokines and chemokines participate in many developmental events by regulating cell growth and differentiation under physiological conditions. However, they are also essential initiators of tumorigenic inflammation [5]. For example, activation of CXCR2 promotes angiogenesis and intratumoral leukocyte infiltration [6,7] and activation of CXCR4 and CCR7 promotes cancer metastasis in several malignancies [8].

Stimulation with cytokines/chemokines and growth factors activates three main intracellular signalosomes closely associated with the regulation of inflammation: janus kinase (JAK)/signal transducer and activator of transcription (STAT), lipid kinase phosphoinositide 3 kinase (PI3 K) and mitogen-activated protein kinases (MAPKs). JAK typically responds to a wide range of interleukins (ILs), and subsequently mediates diverse inflammatory responses depending on the individual dimerization patterns of STATs [9,10]. Inflammatory stimuli activate the three signaling nodes along MAPK pathway − extracellular signal-regulated kinase (ERK), c-jun N-terminal kinase (JNK) and p38, all of which are involved in malignancy of many types of human cancer [11]. Particularly, inflammatory activation of p38 is one of the most common pathways that regulate stability of mRNAs encoding a number of pro-inflammatory cytokines in multiple cell types [12,13]. Thus, the chemical signals in cancer stroma play a critical role in the pathological connection between inflammation and cancer. What factors determine the production of these signals? Growing data uncover the important role of nuclear factor κB (NF-κB), a terminal effector of another important oncogenic signaling axis termed as tumor necrosis factor alpha (TNFα) pathway. Coordinated activation of TNFα axis leads to nuclear translocation and activation of NF-κB, the most important regulator that subsequently transcriptionally activates a number of cytokines [14,15]. These studies indicate that persistent inflammation and carcinogenesis exhibit a mutual-promotion pattern favoring resistance to environmental stress and promoting cell proliferation. Pre-patterning with a chronic inflammatory condition allows timely activation of intracellular survival pathways, such as protein kinase B (PKB), to reinforce cancer cell metabolism and survival.

3. PKB activation drives cancer development

Protein kinase B (PKB, also called Akt) family belongs to the AGC protein kinase subfamily [16]. Three PKB isoforms (PKBα, PKBβ and PKBγ or Akt-1, −2, −3) have been identified in mammals with high sequence-identity and moderate diversity of tissue distribution [17]. PKB is an intracellular kinase, and a break-through discovery was the unraveling of its mechanism of activation involving membrane targeting in response to activated PI3 K. Membrane association of PKB triggers threonine 308 (Thr^{308}) phosphorylation in its kinase domain via phosphoinositide-dependent kinase-1 (PDK1), whereas its biological activity is further enhanced upon phosphorylation on serine 473 (Ser^{473}) in the regulatory domain mediated by mammalian target of rapamycin complex 2 (mTORC2)- or DNA-dependent protein kinase (DNAPK). Due to its direct response to PK3K-induced initial activation, PKB is considered as a major downstream signaling node of PI3 K in the transduction of extracellular signals controlling cellular behavior and fate. Genetic studies in PKB isoform-knockout mice and in a number of transgenic mice models overexpressing constitutively activated PKB isoforms, have indicated a primary physiological role of PKB in the regulation of cell proliferation and survival [18]. This has been confirmed by the progressive discovery that its downstream targets are significantly involved in promoting cell proliferation and survival (anti-apoptosis).

Consistent with its physiological role in development, PKB is commonly hyperactivated in human cancers. Its aberrant activation is contributed via a number of mechanisms including oncogenic alterations of components of the PI3 K pathway, such as mutations or amplification of the PI3 K subunits or inactivation of PTEN [19] and mutation of three PKB isoforms [20–22]. These mutations contribute to a multitude of human cancers, including breast cancer, colorectal cancer, ovarian cancer, lung cancer and melanoma. Excessive activation of the PI3K-PKB pathway, not only promotes cancer cell proliferation and survival, but also likely promotes cell migration and invasion which concur to favor cancer metastasis [23]. For example, a direct link between PKB and cancer cell invasion is highlighted by its downstream target Twist, a key transcriptional regulator controlling cell plasticity through epithelial-mesenchymal transition (EMT), a physiological function frequently hijacked by invasive cancer cells [24]. PKB can initiate EMT through differential phosphorylation on Twist in a context-dependent manner, such as individual extracellular stimuli [25]. Taken together, PKB is a central signaling hub that is responsive to extracellular signal stimulation, and can extensively crosstalk with a number of proto-oncogenic signaling molecules/pathways such as MAPK [26], transforming growth factor-β (TGF-β) [27], vascular endothelial growth factor (VEGF) [28], and ephrins [29]. These orchestrated signaling networks contribute to meet the increased metabolic demand of cancer cells, to promote uncontrolled proliferation and survival, and stimulate migration/invasion. Consistent with the cellular functions regulated by PKB, its hyperactivation is observed predominantly in poorly differentiated tumors that are invasive, fast growing, and resistant to treatment and correlated clinically with poorer outcomes [30].

4. PKB signaling regulated inflammation

PI3 K/PKB/mTOR is one of most frequently deregulated signaling pathways in pathological conditions, including cancer [31]. In addition to directly impacting on cancer cells, cancer cell-intrinsic PKB appears to substantially shape the functionality of the cancer stroma, also called the cancer microenvironment as well [32]. The cancer microenvironment consists of a variety of cell types including cancer-associated fibroblasts (CAFs), pericytes, blood and lymphatic vessels, endothelial cells and tumor infiltrating immune and inflammatory cells [33]. CAFs secrete factors amplifying inflammation and shape the stiffness and density of the cancer stroma while endothelial cells promote angiogenesis to meet the metabolic demand of cancer cells. These two stromal events are critically involved in tumor growth and malignant progression, such as metastasis.

4.1. Immune cell intrinsic role of PKB in motility, activation, differentiation

Tumor infiltrating immune cells represent a major fraction of the cells present in the cancer microenvironment, which significantly influence spontaneous cancer progression and response to anti-cancer

therapy [1,4]. Tumor infiltrating immune cells consist of two major classes: innate immune cells such as NK cells, macrophages and monocytes and adaptive immune cells, namely T and B lymphocytes. The majority of these immune cells are actively recruited along the gradient of chemokines, which are secreted by cancer cells or by cancer-educated immune cells recruited early in the cancer microenvironment. Given the general crucial role of PKB in cell motility [23], it is not surprising to observe a key contribution of PKB in lymphocyte chemotactic migration. Indeed, activation of PKB is induced by S1P (ligand for S1P1) [34], CCL19/CCL21 (ligands for CCR7) [34], CXCL13 (ligand for CXCR5) [34] and CXCL12 (ligand for CXCR4) [35], most probably downstream of PI3 K [34]. Interestingly, PKB dependent phosphorylation of S1P1 is required for S1P1 mediated chemotaxis [36]. Furthermore, KLF2, a key transcriptional regulator of S1P1 expression, is dynamically controlled by a well-known PKB targets, FoxO proteins [37,38]. Notably, activation of PKB in Th17 cells is required for its trafficking towards tumor vicinity [39]. Additionally, engagement of selectins with PSGL-1 and ICAM-1/LFA-1 clustering also lead to intracellular activation of PKB [40], which results in the cytoskeletal rearrangement facilitating lymphocyte rolling and adhesion. Therefore, PKB activation and PKB mediated downstream signaling are likely to be involved in all the aspect of chemotactic migration, trafficking and adhesion of leukocytes to the cancer microenvironment.

In addition to its role in chemotactic migration, immune cell intrinsic PKB has been shown to influence the plasticity of immune responses. After egress from thymus, naïve T lymphocyte circulates as an inactive status. Upon TCR engagement and co-stimulatory signal from CD28, T cells are activated and programmed into an effector status. PKB, being activated during T cell activation and signaling downstream of PI3 K, enhances proliferation of antigen specific mature T cells, protects them from apoptosis and prolongs their longevity [41]. Meanwhile, T cell activation is also balanced by the inhibitory signal from receptors like CTLA4 and PD-1 [42]. Thus while signals from CD3 and CD28 lead to PKB activation within an activated T cells, inhibitory signals from CTLA4 and PD-1 can prevent PKB activation in T cells [43].

The differentiation of CD4 helper T cells is shaped by the dominant transcriptional landscape, namely T-bet, GATA3, FoxP3, RoRr3 signatures for Th1, Th2, Treg and Th17, respectively [44]. PKB-regulated CD4 helper T cell differentiation relies on the functional switch of the activity of driving transcription factors. For instance, PKB directly phosphorylates FoxO1 and FoxO3 [37,38], leading to their cytoplasmic retention thus inhibiting its nuclear transcriptional activity [45]. This further dampens FoxO-dependent transcriptional regulation of T-bet [46,47] and FoxP3 [47–51]. Helper T cell differentiation is accompanied by the activation of unique metabolic programs. Given its key role in cellular metabolism, PKB additionally regulates helper T cell differentiation by impacting on metabolism status. Indeed, activation of PKB up-regulates Glut-1 expression and promotes its membrane localization, thus facilitating glucose uptake in T cells [52]. Additionally, PKB can phosphorylate the glycolytic enzyme hexokinase II, promoting its localization to mitochondria and augmenting its enzymatic activity [53,54]. Importantly, PKB signals with mTOR, a master regulator of global metabolism, thus emphasizing its importance in controlling T cell metabolism [55,56]. CD4 T cells lacking mTOR fail to differentiate into helper or effector cells after activation but instead become FoxP3 regulatory cells [57]. mTOR forms two functional distinctive complexes mTORC1 and mTORC2, which are the downstream and upstream of PKB, respectively[17]. While mTORC1 (downstream of PKB)-depleted T cells fail to generate Th1 and Th17 lineage, mTORC2 (upstream of PKB)-deficient T cells lose their ability to differentiate into Th2 cells [58]. In addition to naïve T cell differentiation, mTORC1 and mTORC2 also substantially influence CD8 effector response and memory status, respectively [59,60]. All these findings highlight a complex paradigm linking the PI3K-PKB-mTOR pathway with T cell differentiation and metabolism.

4.2. Role of tumor-derived PKB activity in inflammation

PI3K kinase itself is a key regulator of chemo-attraction through PIP3 biogenesis [61]; PKB can substantially enhance cell motility in a variety of aspects during cancer progression [23]. While the importance of PI3K-PKB signaling in cancer cell survival, proliferation and motility has been intensively studied in the past, its contribution to the cancer microenvironment, especially in cancer inflammation, has only been progressively unrevealed now [62].

Tumor associated inflammation is a hallmark of cancer and inflammatory condition forms a feed-back loop with cancer progression [63]. For instance, genetic driver mutations that induce cancer, can also initiate the expression of pro-inflammatory- programs that facilitate the development of an inflammatory tumor microenvironment. On the other hand chronic inflammation predisposes to cancer initiation and neoplastic progression by creating a mutagenic and supportive microenvironment, which is well demonstrated by hepatitis B or C induced liver cancer. Tumor associated inflammation is orchestrated by transcriptional regulation of chemokines and cytokines predominantly controlled by nuclear factor-kappa B (NF-κB) and STAT3 pathways [64].

NF-κB is mainly activated by the inflammatory cytokines TNF-α and IL-1β via the toll-like receptor −MyD88 pathway. As a transcriptional factor, NF-κB directly controls the expression of a variety of chemokines and cytokines, which are required for the recruitment of inflammatory cells [65]. For instance, NF-κB stimulates the expression of CCL20, CCL19, CCL5 and CCL17/22, which are predominant chemotactic driver for Th17, dendritic cells, macrophages and regulatory T cells, respectively [5].

NF-κB activity is also tightly controlled via cross-talks with other key intracellular pathways, such as PI3K-PKB-mTOR signaling. PKB has been suggested to directly phosphorylate IKK complex and PKB induces oncogenesis by partially relying on NF-κB signaling [66,67]. In line with this, a subset of NF-κB target genes activated during T cell activation is dependent on PKB activity [68]. Moreover, PKB-dependent mTOR-IKK interaction stimulates IKK activity toward the phosphorylation of IkBα and p65 in PTEN-null/inactive prostate cancer cells [69]. Thus, it is tempting to speculate that PKB might directly influence on NF-κB-dependent chemokine expression to regulate the trafficking of tumor-attracted inflammatory cells.

STAT3 is activated downstream of JAK kinase in response to IL6 family cytokines [70]. STAT3-driven tumor-associated inflammation is highly inter-connected and shares a large fraction of common target genes with the NF-κB pathway [70]. The direct molecular connection between PKB and STAT3 is IL6. It has been suggested that PKB mediated inactivation of FOXO1a down-regulates expression of IL6 [71]. Conversely, IL17 robustly induces IL6 expression and STAT3 activation in a PKB- dependent manner in HCC [72]. These distinct observations seem to be context dependent given the dynamic regulation of IL6 expression via different transcription factors. Notably, Snail, an epithelial-mesenchymal transition inducer involved in cancer migration and invasion, is also transcriptionally regulated by NF-κB [73]. In addition to enhance NF-κB-dependent Snail transcription, PKB activates Snail by phosphorylating and inhibiting GSK3 [74], an upstream inhibitory kinase that prevents the nuclear translocation of Snail [75]. Snail is also capable of transcriptionally up-regulate pro-inflammatory cytokines, such as IL1, IL6 and IL8 [76], which substantially enhances the chemotactic trafficking of both immune cells and cancer cells via the activation of NF-κB and STAT3 pathways.

In addition to chemokines, NF-κB can regulate the expression levels of their receptors, such as CCR5 and CCR7 [77]. Given the activating role of NF-κB by PKB, PKB may also control the expression of these chemokine receptors. Moreover, PKB activation induced by PTEN loss promotes prostate tumor growth and metastasis by up-regulating CXCR4 expression [78]. CXCR4 activation can further boost PKB activity [35,79]. Functionally, PKB activation is required for CXCR4-

induced cancer cell migration [80]. These observations suggest a potential signaling and functional positive feedback loop between PKB activity and chemokine receptors in cancer cell and inflammatory cell migration.

4.3. Role of tumor-derived PKB activity in cancer immune surveillance

The infiltration and accumulation of different immune populations within the tumor vicinity was thought to be crucial to the behavior of cancer cells and the consequent prognosis [33]. Indeed, infiltration of $CD8^+$ T cell, NK cells, and Th1 cells within tumors predicts better prognosis in most cancer types, while infiltration of Th2 cells, Treg, Th17 cells, macrophages and neutrophils is associated with a poorer prognosis [33,81]. Several mechanisms have been proposed, including decreased antigen presenting efficiency in a defined inflammatory microenvironment [82], Treg induced T cell anergy [83] and direct inhibition of immune cells activation via cell-surface inhibitory receptors such as PD-1 and CTLA4 [84].

Notably, escaping from the host immune editing mimics the mechanism(s) of evasive resistance in cancer in response to chemotherapy or targeted therapies. PKB (re) activation was widely observed in therapy resistance development in difference types of cancers. Likely, PKB might substantially influence the immune editing efficacy given its key contribution to immune cell functionality and expression of inflammatory factors. Interestingly, expression of PD-L1, whose binding to inhibitory receptor PD-1 leads to inactivation of immune cells, is tightly correlates and/or regulated by PKB (Fig. 1) [85]. Oncogenic activation of PKB increases the expression PD-L1 in gliomas, lung cancers and colon cancers in an mTOR-dependent fashion [85–87]. Conversely, selective inhibition of PKB with small molecules down-regulates PD-L1 expression [85]. In line with this, interferon gamma (IFNγ), which can activate PKB-mTOR signaling, can also up-regulate PD-L1 expression [88]. Nevertheless, the underlying direct link between PKB and PD-L1 expression as well as in the context of cross-talking with interferon signaling merits further investigation.

4.4. Targeting PKB in tumor-associated inflammation

Hyper-activation of PI3K-PKB signaling is frequently observed in different types of cancers. Activated PKB intrinsically up-regulates NF-κB pathway, which transcriptionally initiates pro-inflammatory networks to build up chronic inflammatory microenvironment. The resultant inflammation can further support tumor cell growth and migration via a combination of enhanced proliferation, favorable metabolic adaption, increased immune surveillance and induced motility via cytoskeleton re-arrangement. Thus, pharmacological inhibition of PKB in cancers not only significantly dampens PKB mediated cancer cell proliferation and metabolic adaption, but also enable an effective immune editing program by favoring the re-activation of immune cells via down-regulating inhibitory signals. Indeed, in a mouse transplantation model, inhibition of PKB with an allosteric inhibitor (PKB inhibitor VIII) reprograms the tumor-infiltrated $CD8^+$ T cells into phenotypic memory cell types coupled with an enhanced and prolonged anti-tumor effect [89]. A similar effect was confirmed with a grafted myeloma mouse model [90]. Additionally, inhibition of PKB with MK-2206 selectively suppressed Treg proliferation and consequently improved anti-tumor activity in a tumor-specific vaccine model [91]. These preclinical studies all point towards a promising strategy with co-targeting PKB for cancer cell specific inhibition as well as improved immune editing.

5. PKB regulated macrophage function

Macrophages are pleiotropic cells with functional plasticity depending on their residing microenvironments. They can be broadly classified into two functional distinct subtypes, namely M1 (classical) and M2 (alternative), in response to different polarization signals [92]. While M1 macrophages are induced by IFNγ or LPS to elicit the production of pro-inflammatory cytokines, mount cytotoxic capacities and orchestrate a Th1 response, M2 macrophages are stimulated by the cytokines IL4 or IL13 to acquire tumor-remodeling capabilities and coordinate a

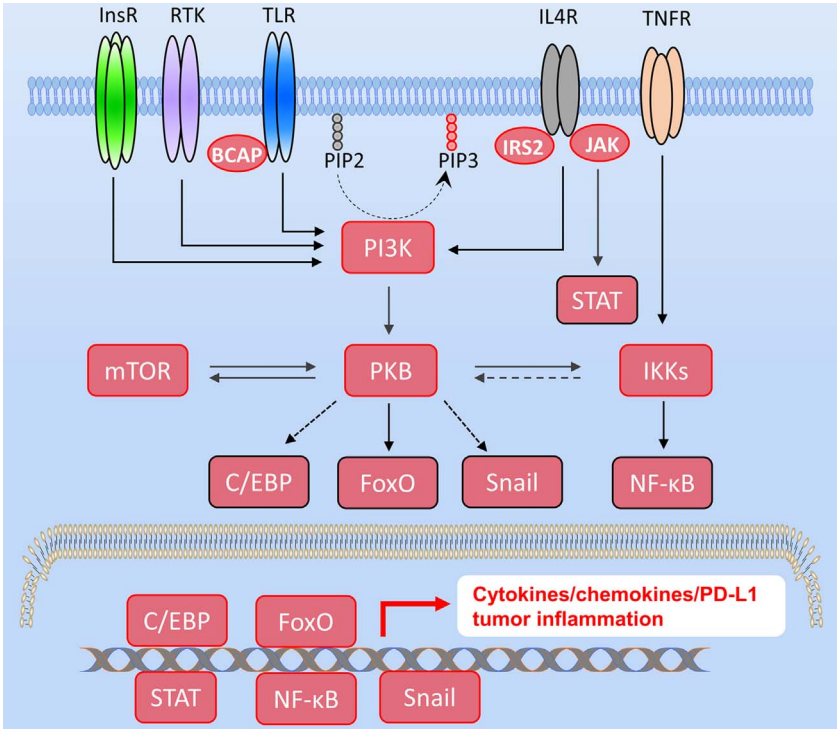

Fig. 1. PKB-mediated signaling cross-talks and its impact on immune checkpoint regulation. Representative extracellular signals such as growth factors, cytokines and chemokines bind to their membrane receptors and activate distinct intracellular pathways involved in tumor-related inflammation. Being a central responding node, PI3K-initiated PKB activation regulates inflammation via upregulating pro-inflammatory factors through cross-talking with its downstream signaling pathways including C/EBP, FoxO, Snail transcriptional factors and IKK/NF-κB axis.

Th2 response. In the context of cancer, M1 macrophages elicit anti-tumoral effects, through cytotoxic activity (in part via cytokine secretion, e.g. TNF, IL6, IL-1β), antigen presentation, and effector T cells recruitment [93]. Conversely, M2 macrophages are pro-tumoral and dampen the tumor inflammation by CCL22-mediated Treg recruitment and arginase-I-mediated suppression of effector T cells [93]. Additionally, M2 macrophages induce cancer cell motility, invasion and metastasis by secreting angiogenic factors and facilitating angiogenesis [93].

Tumor associated macrophages (TAMs) have been widely observed in different types of cancers and often constitute the dominant myeloid cell population in tumors [94]. During tumor initiation and malignant progression, macrophages build up bidirectional interacting networks with tumor cells and other cells of the tumor microenvironment. Macrophages present during the cancer initiation phase are immune active and promote a cytotoxic inflammation [95]. However, once tumors are established, macrophages are educated to become pro-tumoral [95,96]. In line with this, TAMs observed in cancer patients are mostly M2 polarized and correlates with worse prognosis [96,97].

PI3K-PKB-mTOR signaling axis is one of the key pathways controlling macrophage activation and acquisition of context-dependent functions. PKB has been demonstrated to be a crucial effector in macrophage survival [98,99]. Mechanistically, PKB mediates macrophage survival by cross-talking with NF-κB, p38 MAPK and anti-apoptotic signals mediated by Mcl1 and Bcl-xL [98–100]. Notably, IKK deficiency in macrophages results in decreased viability accompanied with reduced activation of PKB [101], indicating a potential feedback between PKB-IKK/NF-κB in the regulation of macrophage survival.

Recruitment of macrophages into the proximity of tumors is driven by gradients of chemokines and cytokines. Of them, CCL2 and CLL5 are the most potent chemokines to attract macrophages and their expression is highly correlated with TAM density in human tumors [102]. CCL2 and CCL5 are produced by tumor cells, CAFs, endothelial cells and even TAM themselves. Of note, global histone H3 Serine 10 phosphorylation has been linked to mediate IKK activation induced CCL2 expression [103,104]. Given a positive input from PKB towards IKK activation, it is tempting to speculate that PKB activation may positively regulate CCL2 expression. Indeed, expression of CCL2 is tightly controlled by NF-κB signaling partially through PKB activation in a PTEN-loss brain tumor model [105]. Furthermore, in an EMT induced immunosuppressive condition, CCL2 expression is regulated by the transcription factor Snail [106], which itself is negatively regulated by GSK3β, a direct target of PKB. Interestingly, PKB is also activated in response to CLL2 [107], indicating a positive forward signaling loop between PKB activation and CLL2 expression. Colony stimulating factor (CSF-1) is another main driving cytokine for macrophage recruitment [102], which is transcriptional controlled by the SWI/SNF complex [108]. Although members of the SWI/SNF chromatin-remodeling complex have been shown to interact with and be phosphorylated by PKB [109], a direct contribution of PKB in the context of SWI/SNF mediated CSF-1 expression is still missing. Nonetheless, PKB has been shown to be required for macrophage chemotaxis in response to both CSF-1 and CCL2 [110].

Macrophage polarization programs directly shape the functionality of macrophages. Notably, both M1 and M2 polarization signals can potently activate PKB. Mechanistically, in the context of LPS mediated M1 activation, B-cell adapter for PI3K (BCAP) bridges TLR4 signal to PI3K activation [111], which activates downstream PDK1-PKB-mTOR. In the scenario of IL4 induced M2 polarization, IL-4R recruits the adaptor protein Insulin receptor substrate 2 (IRS2) [112], which engages and activates PI3K resulting in the activation of PKB. Activation of PKB in response to polarizing signals suggests a potential and crucial contribution in macrophage activation. Indeed, PKB appears to promote M2 polarization, as inactivation of PKB leads to a defect of IL4-induced M2 polarization in TSC-deficient macrophages [113]. This is further supported by a PKB haplodeficient pulmonary fibrosis model [114]. However, in line with M1 activation signals activating PKB, several studies also demonstrate that PKB indeed is critically involved in promoting M1 macrophage activation [115,116]. The clear discrepancy might come from an isoform specific effect of PKB in experimental context. Indeed, in an isoform specific deficient model, it is observed that while PKBα inhibits M1 activation and promotes M2 polarization, PKBβ enhances M1 activation and suppresses M2 polarization [115]. Another layer of regulation of macrophage polarization contributed by PKB might come from the downstream effectors. M1 and M2 activation and cytokine production programs are transcriptionally controlled by NF-κB/IRFs and STAT6 signaling, respectively [117,118]. As discussed above, PKB positively contributes to NF-κB activation in T cell mediated inflammation. Similar results were observed within macrophages as well [116], indicating a promoting role of PKB in M1 activation. Interesting, an inhibitory effect of PKB has been also observed in LPS induced and NF-κB-mediated M1 polarization in human monocytes, most probably via inactivation of MAPK signaling [119]. Additionally, activation of PI3 K and PKB is required for nuclear translocation of IRF7 and type 1 interferon production [120], indicating a potential importance of PKB in the regulation of IRF mediated M1 activation program. Furthermore, FoxO1 induced M1 macrophage activation can be dampened via an inhibitory phosphorylation of FoxO1 by PKB [121]. Notably, PKB can tightly control the expression of C/EBPβ [115], a transcription factor implicated in both M1 and M2 activation. Taken together, although macrophage polarization is associated with PKB activation, PKB mediated macrophage activation is highly context and isoform dependent.

Targeting TAMs, especially functional switching from pro-tumoral M2 to anti-tumoral M1, is a promising strategy in anti-cancer therapies. Pharmacologically targeting PKB in TAMs might not provide a consistent and desired effect in terms of macrophage polarization given the dynamic and context dependent role of PKB in macrophage activation. Nevertheless, targeting PKB might offer a potential option for depletion of TAMs by accelerating their turnover and preventing the chemotactic migration of macrophages to the vicinity of tumors.

6. Summary

Tumor related inflammation and genomic mutational landscape collaboratively shape tumor progression and therapy response. Among the key cellular pathways activated in tumorigenesis, hyperactivation of PI3K-PKB signaling in tumors not only strongly promotes cancer cell proliferation, survival and motility per se, but also substantially induces an inflammatory tumor microenvironment, which subsequently influences behavior of cancer cells (Fig. 2). Thus, targeting PI3K-PKB axis represents a promising strategy to enhance T cell mediated immune editing in tumors. Recent exciting studies with immune checkpoint blockers suggest a potential therapeutic combinatorial option with PI3K-PKB inhibitors, which might release the immune-suppressive role of TAMs [122]. Similar evidences have been obtained from the combination of checkpoint inhibitory molecules targeting T cells with CSF1R inhibitors targeting macrophage [123]. However, a context- and isoform-dependent role of PI3 K and PKB in inflammation and immune response call for caution when considering combination therapies with PI3 K or PKB inhibitors. A second key issue with such combination therapy is the therapeutic window, namely to enhance the anti-tumor efficacy while maintain the side-effect acceptable. A deeper understanding the molecular mechanism of PI3K-PKB target therapy in the context of tumor related inflammation and immune checkpoint inhibition is warranted and will be essential in order to pave the way for more effective cancer therapies.

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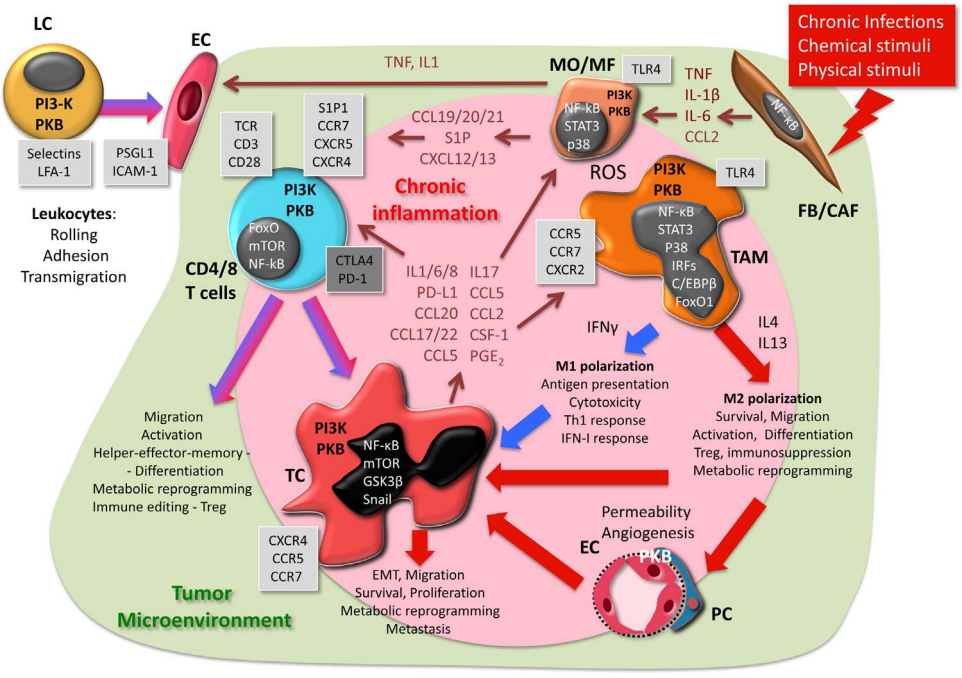

Fig. 2. Cellular effects of PKB in cancer-related inflammation. External persistent stimuli (infectious, chemical or physical) as well as oncogenic signals in tumor cells can initiate chronic inflammation. Additional immune/inflammatory cells are recruited from the blood (T/B cells, NK cells, monocytes, neutrophils) to further sustain chronic inflammation. M2-polarized tumor activated macrophages are main drivers of tumor cell invasion, survival, angiogenesis and immunosuppression. PKB plays key roles in virtually all cells of the tumor microenvironment to promote inflammation and tumor progression, by controlling expression of chemokines and cytokines, as well as mediating some of the effects downstream of their receptors. The PKB effects, however, is contextually regulated by the activation/differentiation state of the effector/target cells and by the concurrent activation of other signaling pathways through additional factors. The list of interactions/effects is non- exhaustive, see text for full explanation. Brown arrows; communication through factors and chemokine; thick arrows, global functional effects (blue, inhibitory effects; red, stimulatory effects). Abbreviations: EC, endothelial cell; EMT, epithelia-to-mesenchymal transition; F/CAF, fibroblast/cancer activated fibroblast; LC, leukocyte; MO/MF, monocyte/macrophage; PC, pericyte; TAM, tumor associated macrophage; TC, tumor cell. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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