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RETINOBLASTOMA PROTEIN IN INFLAMMATION: A REVIEW

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ABSTRACT: Inflammation is a host immune response initiated by the activation of inflammatory cascades resulting from any tissue injury. During the inflammatory response, multiple inflammatory mediators are released to restore the organ function and integrity by activating various inflammatory mediators. The presence of these molecules in the tumor microenvironment led to studies on the molecular pathways that are modulated during the inflammation to cancer transition. RB pathway is one such signaling pathway becoming more recognized in the microenvironments of pancreatitis and pancreatic ductal adenocarcinomas. RB1 is known to have multifunctional roles in the cellular growth and development processes, including apoptosis and autophagy. The RB protein in a dephosphorylated state negatively regulates the cell cycle at different checkpoints, thereby influencing the G1 to S phase progression. Besides its cell cycle activity, recent reports suggest that RB protein has a role in the pathogenesis of inflammation. The deregulation in the expression of RB protein is said to play an active role in stimulating the pro-inflammatory molecules, consequently resulting in inflammatory responses during cancer progression. This review article focuses on the RB protein status in inflammation providing collective information on new molecular targets for early intervention.

INTRODUCTION: Inflammation is a defensive response of the human body to the stimulus of cellular damage and tissue injury. Generally, the inflammatory responses are characterized by edema, pain, redness, and fever. These responses occur due to the activation of various inflammatory mediators such as cytokines, chemokines, and other gaseous molecules [1]. Several signaling mechanisms and pathways regulate the activity of these signaling molecules. Any disturbance in the regular physiological function of the signal transduction pathways may result in adverse inflammatory reactions [2].

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The tumor suppressor activity of the retinoblastoma protein (RB) renders it responsible for the suppression of solid tumors. The RB is a crucial cell cycle regulator that influences the G1/S phase transition by modifying the activity of E2F transcription factors. The E2F activity depends on the phosphorylation status of the RB protein. RB deregulation during cancer progression enhances some characteristics of malignancy, including altered drug sensitivity and a return to the undifferentiated state. Additionally, it has been proposed that RB directly regulates the pro-inflammatory signaling in inflammatory response [3].

Recently, studies are being carried out to unravel the molecular pathways and signaling mechanisms linking cancer and inflammation. Cancer-associated inflammation is said to be the seventh hallmark of cancer [4]. In some cases, inflammatory responses may influence the risk of acquiring cancer and associated malignancies in certain

organs. In addition to the existing mechanisms related to cancer-related inflammation, the inflammatory mediators may induce genetic instability in cells [5]. Such random genetic alterations get accumulated, resulting in the development of cancer [6]. Moreover, inflammation-driven cancer mechanisms such as the RB pathway are gaining attention in recent times. Emerging reports suggest that RB plays a prominent role in inflammation-driven cancers, especially in pancreatitis-associated fibrosis [7-9]. In view of the fact that RB deregulation plays a significant role in various cell cycle events, the idea of investigating the interactions of RB during inflammatory conditions seems promising. However, there are only a handful of research evidence to support the role of RB in inflammation to date. Therefore, this review aims to compile the available studies to provide more insight into understanding the RB signaling interactions in inflammatory conditions.

1. Physiological Role of RB Pathway: The classical role of RB is described as cell cycle regulation, which makes it crucial for proliferation and more diverse cellular mechanisms, including its tumor suppressor activity, genomic stability, and apoptosis [10]. It is understood that various interactive molecules regulate the multifunctionality of the RB protein. The comprehension of these communications of RB protein comes from the basic understanding of the molecular structure of the RB protein [10].

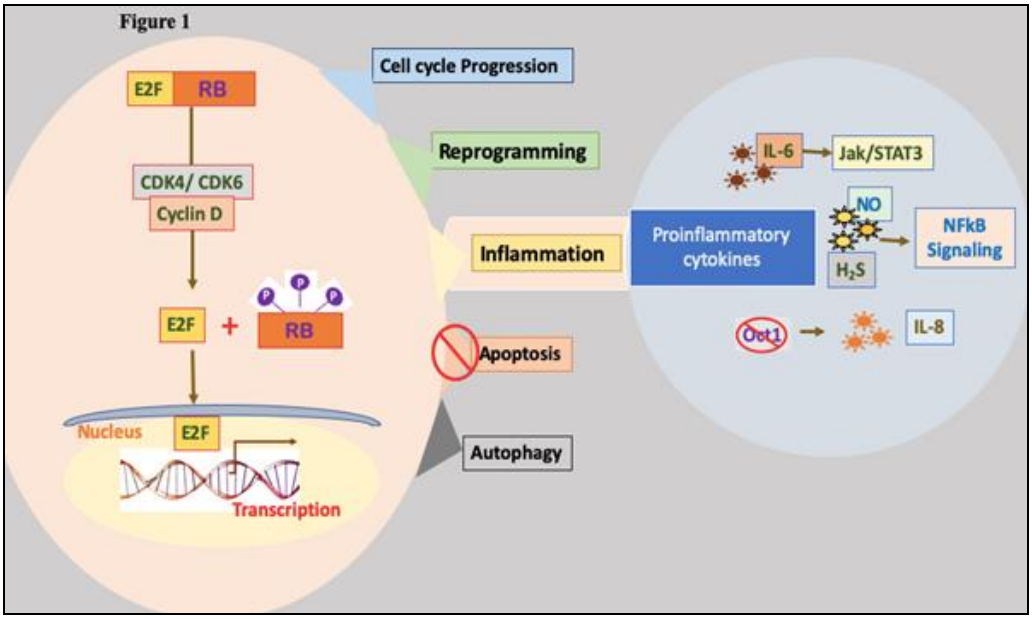

FIG. 1: PHYSIOLOGICAL IMPLICATIONS OF RB IN PRO-INFLAMMATORY SIGNALING

In humans, the RB protein is composed of 928 amino acids structured into 3 domains. The central domain known as 'pocket'interacts with the viral oncoproteins comprising of 2 subdomains A and B. These subdomains knit themselves into a single unit interacting among themselves through capacious non-covalent interfaces. In addition, it possesses two structural folds that possess the amino-terminal domain (RB-N), which is slightly similar to the pocket. The RB's intrinsically disordered carboxy-terminal domain (RB-C) comprises the last 150 amino acids [11, 12]. The RB protein is encoded by the RB Transcriptional Corepressor 1 or Retinoblastoma 1(RB1) gene that promotes the transcriptional repression of the E2F network. A mitogenic signal stimulates the formation of the cyclin D–CDK4/6 complexes that promote RB phosphorylation liberating E2F transcription factors; consequently, the cell progress from G1 to S phase [13]. The dephosphorylation of RB1 activates and forms E2F complexes that down-regulate the transcription resulting in cell cycle arrest. The deregulation in the RB pathway has detrimental effects on most of the cancer cells [14, 15]. Mutations in RB are mostly found pathogenic in several tumor tissues, namely retinoblastoma, pancreatic adenocarcinoma (PDACs), osteo-sarcoma, small cell lung carcinoma, and so on. It is also frequently seen that INK4A mutations are found in PDACs and non-

small cell lung carcinoma, while CCND mutations are predominantly detected in breast cancer [15, 16]. Further ahead, the RB hyperphosphorylation leads to repression of the mTORC2 associated AKT signaling resulting in hypersensitivity to chemotherapy. In addition, extensive evidence supports the alternating roles of p53 and E2F1 during RB deregulation [17]. Besides these molecular signaling events, RB also remodels the chromatin construction, which is known to influence the altered gene transcription mechanisms in various disorders [18]. The essence of the above evidence is that any faulty communications amongst the various interactive genes or components of RB signaling such as CDK4/6, INK4A, CCND, E2Fs lead to uncontrolled cellular proliferation and physiological events. Additionally, the RB/E2F complexes modulate genes responsible for innate immunity and cytokine signalling [19].

On the other hand, the multiple binding abilities of RB protein allow E2F-independent functions with the extra-nuclear partners. The E2F-independent functions of RB are relevant to RUNX2-mediated cell differentiation, negative regulation of p27 related cell cycle arrest, and p27-dependent apoptosis [20]. However, RB in acute inflammation's role is more under-investigated compared to its cell cycle functions and other physiological events. Acute inflammation is simply an immune response to any tissue injury. It is indicated by the release of various inflammatory mediators like cytokines, chemokines, and free radicals as a counter-strategy to combat inflammation and microbial clearance from the injury site. Unlike the inflammation in its acute form, chronic inflammation interrupts the active functioning of surrounding cells as the recurring cytokine surge affects the tissue homeostasis and resolution of the initial inflammatory response, possibly progressing towards cancer. The discrete ability of RB to control the cell cycle through phosphorylation is varied as a consequence of exposure to inflammatory mediators [3].

2. RB Pathway Components in Inflammation: Historically, the cyclin-dependent kinase system was referred to as the molecular powerhouse that controls the cell cycle entry/exit, which holds till date. The meddlesome point mutation Arg 24 Cys in the CDK4 gene helps the cell to bypass the INK4 inhibition promoting cell cycle progression [21]. These genomic modifications facilitate CDK functionality related to CDK4 mutations in epithelial malignancies and CDK6 mutations in mesenchymal tumors. But the more advanced investigation into the CDK activities has led to the discovery of CDK cell cycle-independent biological functions. One such function is the pro-inflammatory role of CDK4 and CDK6 [22]. Although the essentiality of CDKs in inflammation has been deduced, a discrete molecular mechanism to address its function in this regard is lacking. The research on the CDK-cyclin system proffers a whole new world of the agnostic molecular tools and technologies against inflammation at our hands which is waiting to be brought into the spotlight. As a first step, the CDK antagonists that effectively block the RB function such as Palbociclib are used as an adjuvant therapy to treat breast cancer that predominantly rely on the pro-inflammatory tumor microenvironment [23].

An inflammatory pathological condition manifests prior to the tumorigenesis process; many tumors take advantage of the inflammatory species in the microenvironment to progress into a malignancy. Simply put, the microenvironment serves as a pool of sufficient mitogenic growth factors, extracellular adhesion molecules, and proangiogenic effectors responsible for metastasis transition. Considering the above fact, the RB inhibition achieved through CDK blockage may be a potential futuristic platform for developing therapeutic strategies against acute and chronic inflammatory conditions [24].

As discussed in section 2, the multifunctional ability of RB protein creates a large window of specific targets against a variety of molecular events that occur during inflammation-driven cancers. In concordance, many pre-clinical studies indicate that the histone deacetylase (HDAC) inhibitors possess anti-inflammatory effects based on the cell type and stimulating molecules. The trichostatin A is a potent HDAC antagonistic agent that suppresses-lip poly-saccharide (LPS) or IL-1β or interferon γ-stimulated nitric oxide synthase levels in mouse macrophage-like cells. However, it was found that it promotes the LPS-induced nitric oxide synthase expression in rat microglial cells, confirming the tissue-specific role of HDAC

inhibitors [25]. Also, trichostatin an up-regulated LPS-induced IL-8 but decreased the expression of IL-12 in human lung epithelial cells [26]. In contrast, an HDAC inhibitor named ITF2357 suppressed the pro-inflammatory activity of cytokines IL-1, TNF-α, and IFN-γ in peripheral blood mononuclear cells [27]. Interestingly, when cells were stimulated with IL-12 plus IL-18, ITF2357 reduced IFN-γ and IL-6 production without affecting IL-1 or TNFα expression [27]. The pathophysiological relevance of these processes explains that the prevention or resolution of inflammation can be influenced by the interactions of RB with a variety of inflammatory mediators.

3. Effect of RB on Inflammatory Mediators: Macrophages are the immune cell which gets activated first to combat pathogens by triggering an inflammatory response and innate immunity. The monocytes from the hematopoietic origin give rise to the macrophages. Monocytes in the systemic circulation infiltrate into the tissues that undergo differentiation and mature into resident macrophages.

There are 2 distinct macrophage phenotypes, namely M1and M2 macrophages. M1 phenotype is activated by the interferon (IFN-γ) associated microbial inducers like LPS. Upon stimulation, these M1 macrophages secrete pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF-α), interleukins (IL1, IL6, IL12), chemokines (Cxcl9, Cxcl10, and Cxcl5), gaseous mediators (hydrogen sulfide (H2S) and nitric oxide (NO)) and reactive oxygen species [28]. On the other hand, M2 macrophages are stimulated by the interleukins (IL4/IL13) that promote the secretion of anti-inflammatory cytokine (IL-10).

Unlike M1, M2 cells possess poor antigen-presentation; nevertheless, it is responsible for antigen clearance, tissue homeostasis, suppression of pro-inflammatory responses. In recent times, studies suggest that innate immunity modulation is one of the primary activities of the tumor suppressor proteins. Such that, the tumor suppressor RB protein controls the innate immune response even during the viral invasion. RB is crucial NF-Kb activation while conferring immunity against virus infection [29]. RB activates the toll-like receptor (TLR3) as the E2F1 binds to the TLR3 promotor, which senses double-stranded RNA virus infections [30, 31]. However, the diverse mutational mechanisms of the RB pathway in different tissues make it difficult to understand RB's molecular interactions that affect several physiological events during inflammation.

3.1 RB-IL6 Axis: RB inactivation enhances pro-inflammatory signaling through stimulation of the interleukin-6/STAT3 pathway, which directly promotes various malignant features of cancer cells [32]. More than 300 proteins have been identified as possible binding partners of RB [5].

The variability in these binding partners could explain the multifunctional aspects of the RB protein. The mitochondrial superoxide synthesis initiated by RB inactivation enhances the IL-6 secretion via c-Jun N-terminal kinase (JNK) signaling in MCF-7 breast cancer cells [33]. This RB-IL6 axis influences the mitochondrial activity, which modulates the self-renewal and T cells hyperactivation, which causes a fatal immune response due to an upsurge in IL6 production. The oxidative stress and RB inactivation associated DNA damage-induced "cytokine storm" is attenuated by tocilizumab which produces an anti-IL6 antibody to combat the IL6 upsurge [34].

3.2 IL8 and RB Activity: It is widely reported that the IL8 recruits the neutrophils in a tumor microenvironment playing a major role in neutrophil tissue infiltration [35]. In recent times, the decrease in tumor cell survivalis attributed to RB protein, which is dependent on IL8 associated neutrophil activity. In bladder carcinoma cells, RB activity elevates IL8 secretion when compared to RB-defective cells [36]. This RB-mediated IL8 upsurge is a result of decreased Oct-1 activity, which originally possesses the function of repressing IL8 promoter [36]. Therefore, the above reports indicate that the RB enhances the neutrophil migration is mediated through IL8.

3.3 Gaseous Mediators: RB also enhances the pro-inflammatory effect of H2S mediated by NF-RB in mice with acute pancreatitis and associated lung injury [9]. In other studies, RB hyperphosphorylation initiated by NO release is mediated *via* guanosine 3′,5′-cyclic monophosphate (GMP) signaling PI3K/AKT mechanisms and

mitogen-activated protein kinase (MAPK) pathways [37]. Many interleukins and macrophage migration inhibitory factor (MIF) mediate RB hyperphosphorylation during inflammation-driven fibrosis [38]. Moreover, it is reported thatNO dependent RB hyperphosphorylation is responsible for the production of nitrate and nitrite, contributing to disease progression in colitis [39].

Also, the RB inactivation initiated by NO is crucial for human colon cancer cell hyperproliferation. Emerging studies provide sufficient evidence to consider RB interactions with gas molecules like H2S and NO as potential molecular targets against inflammation-associated carcinogenesis.

4. RB Pathway Regulates Cell Death Mechanisms: Besides its cell cycle functions, any apoptotic event initiated by a cell injury or DNA damage could be RB dependent. RB, E2F and the tumor suppressor p53 control certain death-associated proteases involved in the apoptosis [40].

However, the IL-converting enzyme-like proteases destroy RB activity by cleaving the aspartate rich loci during the cell death processes. Further, Bcl-2 also partially inhibits apoptosis by regulating the RB phosphorylation [41]. RB associates with the Bcl-2 associated athanogene 1 (BAG-1) protein promoting NF-κB activity in breast cancer cells [42]. The anti-apoptotic character of RB was revealed; when RB function was restored in RB1-deficient cancer cells, reduced apoptotic events were triggered by P53 up-regulation and ionizing radiations. Additionally, E2F drove Bcl-2 repression releases Beclin-1-Bcl-2complexwhich results in autophagy [43].

Moreover, RB dephosphorylation by cyclin-dependent kinase inhibitors can interrupt the extrinsic apoptosis mechanism. RB dysfunction regulates the molecular fusion between the autophagic and lysosomal complexes that eventually cause accumulation of the autophagosomes, activation of caspase 8, and further initiating apoptosis [44]. More investigations have confirmed that chemotherapy-associated autophagy may be responsible for resistance against apoptosis. Autophagy is a recycling process of the damaged organelles that wrongly aid in cancer cell survival, interrupt apoptotic mechanisms, and result in resistance to chemotherapy [45]. Further, studies show that RB acts as a molecular regulator controlling the reversible transition of autophagy to apoptosis and a biomarker to identify therapy resistance in glioblastoma. Supportively, Biasoli, Deborah *et al.* reported that RB dysfunction blocks the Etoposide-induced autophagic flux, which induces apoptosis in glioblastoma cells [46, 47]. Furthermore, RB-dependent autophagy and senescence work simultaneously. The cell cycle arrest is initiated by autophagy along with the release of senescence-inducing interleukins. However, the administration of autophagic inhibitors reduces the senescence activity in the cells [46]. In addition, TGF-β initiates RB/E2F1-dependant autophagy in cancer cells, affecting many autophagic genes and their functions [48].

5. RB-Potential Target against Inflammation: Given the fact that RB regulates the expression of pro-inflammatory genes mediated by microRNAs (miRNA or mir), it is often overlooked in inflammatory conditions. An overall miRNA expression analysis in sarcoma and breast cancer cell lines revealed that RB inactivation remarkably down-regulated mir-140 expression.

Although there is still no clarity about the molecular mechanism behind the same, more supportive studies are reported in recent times. One such study reveals that mir-140 down-regulated by RB inactivation results in increased pro-inflammatory activity of IL-6 mediated via STAT3 [49]. Also, the elevated levels of IL6 due to RB inactivation in luminal- cancer cell type induce stem-like character and hormone-independent growth.

Furthermore, RB phosphorylation releases E2F directly associated with cyclo-oxygenase (COX2) protein in basal-like breast carcinoma [50]. Indeed, it is also reported that the RB–E2F complexes down-regulate the inflammatory cytokine and chemokine levels, including IL-8, CXC ligand 1, and CXC ligand 232. In concordance, we have previously shown that RB inhibition mediated by NF κB signaling restores the organ integrity in cerulein injured pancreatic and lung tissues as well as it regulates pancreatic stellate cell activation in acute pancreatitis driven fibrosis [9]. This evidence unravel

the fact that RB dysfunction or inactivation contributes to disease progression by acting *via* cell-extrinsic mechanisms like activation of pro-inflammatory cytokine cascades. A few reports support the fact that RB hyperphosphorylation-induced IL6 activation can be a molecular target against inflammation. This is confirmed by using tocilizumab, an anti-IL6 antibody that specifically has a therapeutic effect on RB-deficient breast cancer (MCF-7) cells [33].

Furthermore, the mitochondrial RB promotes apoptosis by BAX activation as a response to TNF-α release in cells [51]. However, the question of whether RB could be a potential therapeutic target against inflammation remains unanswered as more investigations are needed to deduce the molecular mechanisms involved in the anti-inflammatory actions of RB signaling.

CONCLUSION: More evidence suggests that the tumor suppressor protein like RB possesses a non-transcriptional role, such as hyperactivation of pro-inflammatory mediators contributing to innate immunity [3].

Although RB protein's transcriptional regulation of the inflammatory cytokinesis was investigated, the molecular interactions among the cytokine signaling and RB pathway remain unclear. Additionally, macrophage (M1/M2) polarization has been shown to be modulated by the tumor suppressor RB protein. These reports suggest the possible effects of RB signaling on inflammation which could be a futuristic target to discover novel therapeutic interventions.

Since, many of the molecular cancer mechanisms also play a crucial role in inflammation, the cancer therapeutic agents might have a possible role in the attenuation of inflammation.

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