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Review

Inflammation as a driver and vulnerability of KRAS mediated oncogenesis

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ABSTRACT

While important strides have been made in cancer therapy by targeting certain oncogenes, KRAS, the most common among them, remains refractory to this approach. In recent years, a deeper understanding of the critical importance of inflammation in promoting KRAS-driven oncogenesis has emerged, and applies across the different contexts of lung, pancreatic, and colorectal tumorigenesis. Here we review why these tissue types are particularly prone to developing KRAS mutations, and how inflammation conspires with KRAS signaling to fuel carcinogenesis. We discuss multiple lines of evidence that have established NF-κB, STAT3, and certain cytokines as key transducers of these signals, and data to suggest that targeting these pathways has significant clinical potential. Furthermore, recent work has begun to uncover how inflammatory signaling interacts with other KRAS regulated survival pathways such as autophagy and MAPK signaling, and that co-targeting these multiple nodes may be required to achieve real benefit. In addition, the impact of KRAS associated inflammatory signaling on the greater tumor microenvironment has also become apparent, and taking advantage of this inflammation by incorporating approaches that harness T cell anti-tumor responses represents another promising therapeutic strategy. Finally, we highlight the likelihood that the genomic complexity of KRAS mutant tumors will ultimately require tailored application of these therapeutic approaches, and that targeting inflammation early in the course of tumor development could have the greatest impact on eradicating this deadly disease.

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1. Introduction

The RAS family of oncogenes was one of the first to be identified as mutated in human cancer. But despite extensive investigation of the signaling networks that RAS activates to promote cellular transformation, effective therapy has yet to be discovered either against RAS itself or its multitude of downstream targets. Since mutations in KRAS are frequently observed in three of the leading causes of cancer deaths: lung adenocarcinoma (LUAC), pancreatic ductal adenocarcinoma (PDAC), and colorectal carcinoma (CRC), the ability to target KRAS effectively would almost certainly reduce the morbidity and mortality from these common cancers [1].

KRAS-driven carcinogenesis is tightly linked with tumor promoting inflammation, which is increasingly recognized as target for therapeutic development. Activating mutations in KRAS endow epithelial cells with the capacity to survive and expand in this setting, often fueled by the same cytokines that are attempting to recruit inflammatory cells and fend them off [2]. Indeed, the most common tumors in which KRAS mutations are observed arise from the epithelial linings of organs – lung, pancreas, and colon – that sustain both mutational and inflammatory insults over the course of time (Fig. 1). In addition, KRAS-driven cancers are not uniform diseases. Tissue specificity shapes the microenvironment in which the cancer develops, co-mutation of different tumor suppressor genes can modify how inflammatory signals downstream of KRAS are elaborated, and a variety of other factors such can influence the unique immune cell ecosystem that each cancer is associated with. Thus, therapies that target tumor promoting inflammation downstream of KRAS will likely need to be tailored further based on certain genomic or immunologic contexts.

In this review we will focus specifically on the recent data that supports a critical role of inflammation in oncogenic KRAS mediated tumor development and maintenance, and how targeting inflammatory signaling pathways will likely be a necessary component of effective KRAS targeted therapy. First we will review the evidence for inflammatory signaling in promoting KRAS-associated lung, pancreatic, and colorectal carcinogenesis. Next, we discuss how cell intrinsic factors such as levels of basal autophagy may influence the relative engagement of immune signaling pathways, and how differences in the tumor immune microenvironment could influence immune targeted therapy. Finally, we end with a discussion of therapeutic considerations, and how developing combinations which incorporate drugs that counteract this tumor promoting inflammation may ultimately help to make KRAS-driven cancers a manageable disease.

2. Inflammation and KRAS-driven lung adenocarcinoma

Oncogenic mutations in KRAS are observed in approximately 1/3 of cases of LUAC and are strongly associated with smoking [3]. The effect of tobacco associated mutagens and chronic inflammation in fueling KRAS-driven lung cancer has been well documented in mouse models. For example, exposure to the tobacco carcinogen 3-methylcholanthrene (MCA), particularly when followed by induction of chronic inflammation with the non-carcinogenic pneumotoxin butylated hydroxytoluene (BHT), triggers a high frequency of murine lung cancers with Kras codon 12 mutations that mimic the spectrum observed in human LUAC [4]. More recent whole exome sequencing from mouse lung tumors arising from treatment with methyl-nitrosourea (MNU) also revealed common mutations in Kras codon 12, differing from other models that involve direct genetic activation of a $Kras^{G12D}$ allele, in that the former is dominated by high mutational load while the latter are associated with aneuploidy [5]. This study further examined mutational profiles following urethane treatment, another chemical carcinogen utilized in mouse lung cancer models that induces inflammation and NF-κB activation [6]. In contrast to MNU, urethane caused frequent $Kras^{Q61L}$ and $Kras^{Q61R}$ mutations, and a different mutational spectrum in general. Together, these studies highlight the fact that different mutagenic insults, coupled with inflammation, can promote distinct but common paths towards oncogenic KRAS activation in LUAC.

Genetically engineered mouse models (GEMMs) of Kras-driven lung cancer have been instrumental in defining specific signaling components, including NF-κB, STAT3, and secreted cytokines, that fuel oncogenesis. Although they typically lack the high mutational load and more faithful evolution of carcinogen induced lung tumors, these models have nonetheless helped to define oncogenic KRAS biology in vivo and its collaboration with commonly mutated tumor suppressors. These models have also enabled testing of genetic requirements and novel therapeutics, given the relatively short latency of lung tumor development. Multiple studies have defined an important role for NF-κB signaling the aggressive lox-stop-lox (LSL) $Kras^{G12D}$;$p53^{Flox/Flox}$ (KP) mouse model of lung cancer. Expression of the IκB super repressor gene inhibited tumorigenesis in this model [7], as did genetic deletion of the p65 subunit or chemical inhibition of IκB kinase (IKK) activity [8,9]. In contrast, studies of STAT3 signaling have suggested a more complex role for this key downstream mediator of cytokines in KRAS-driven tumorigenesis. Lung epithelial specific knockout of Stat3 paradoxically increased inflammation and Kras-driven tumorigenesis following urethane treatment, and cooperated with oncogenic Kras in tumor initiation, but was required in both instances for sustained tumor growth [10]. Another study further demonstrated that Stat3 disruption enhanced lung tumorigenesis downstream of oncogenic Kras, though showed mechanistically that this resulted from dysregulated NF-κB signaling [11]. Specific deletion of IL6 in mouse lung epithelia has yielded similar paradoxical results. In two separate studies, IL6 deletion combined with $Kras^{G12D}$ mutation promoted lung tumorigenesis but impaired tumor growth [12,13], although the effect on tumor growth required intact p53 [12]. However, a more defined role for IL6 in promoting lung cancer pathogenesis was recently demonstrated in the LSL-$Kras^{G12D}$;$Lkb1^{Flox/Flox}$ (KL) model [14], an equally if not more aggressive model compared to KP mice [15]. In this setting, Lkb1 inactivation shifted the immune microenvironment towards the accumulation of neutrophils, which exhibited T cell suppressive activity through the release of multiple cytokines including IL-6. In this model tumor growth was inhibited by treatment with a neutralizing IL-6 antibody [14]. Together, these studies demonstrate a key role for these inflammatory signals in fueling KRAS-driven lung cancer, but highlight feedback compensation between STAT3 and NF-κB signaling and tumor suppressor background as important issues to consider.

3. KRAS signaling and inflammation in pancreatic ductal carcinogenesis

PDAC is associated with the highest frequency of KRAS mutations of any tumor type [16]. Similar to LUAC, inflammation plays a key role in its pathogenesis, as lifetime risk of developing PDAC in patients with familial pancreatitis syndromes approaches 69-fold that of the general population [17]. The most common causes of hereditary pancreatitis involve germline mutations in PRSS1, encoding trypsinogen, or SPINK1, a serine protease inhibitor that limits trypsin activity, suggesting that chronic exposure of the pancreas to its own damaging projects may be a major etiologic factor in pancreatic carcinogenesis [18]. In contrast to $KRAS^{G12C}$ transversion mutations, which are associated with smoking and commonly found in LUAC, PDAC is commonly associated with $KRAS^{G12D}$ or