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Conceptual Paper

Inflammasome and its Component NLRP3 Plays a Major Role in Tumorigenesis

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Chronic inflammation plays a crucial role at different stages of tumor development, including initiation, invasion and metastasis [1-4]. Many cancers are associated with chronic inflammation, for instance, hepatocarcinoma from Hepatitis B or C virus infection, gastric cancer due to *Helicobacter pylori* and colorectal cancer from ulcerative colitis [5,6]. Altered cell signaling pathways involving kinases and their downstream transcription factors have been established as the major contributors associated with inflammation-induced carcinogenesis [7]. Inflammation, particularly involving inflammasomes, modulates carcinogenesis through secretion of various inflammatory cytokines. Inflammasome is an important multimolecular complex formed by NOD-like receptor (NLR) family members that regulates inflammatory immune responses by activating proteolytic enzyme caspase-1 [8]. Activation of inflammasome via canonical pathway promotes caspase-1 dependent maturation of proinflammatory cytokines IL-1β and IL-18 as well as induces pyroptotic cell death in response to pathogen-associated molecular patterns or endogenous danger signals [9]. Proinflammatory cytokines attracts a myriad of immune cells such as neutrophils, macrophages, monocytes and leukocytes to organize a local immune network within tumor microenvironment. In inflammatory cells, caspase-1 activation can initiate pathways leading to sterile inflammation, production of trophic factors required for cancer cells and their stroma [10].

Different mechanisms take part in inflammation-induced carcinogenesis. Inflammation causes damage to the cells and tissues which can lead to tumor initiation and development. Inflamed tissues generate reactive oxygen species and reactive nitrogen species which are toxic to DNA [11]. Oxidative DNA damage induces mutations in oncogenes and tumor suppressor genes. Under high oxidative stress, other cellular components such as lipids generate reactive intermediates that form DNA adducts and inactivate various cancer suppressor genes like PTEN and STK11 [12]. Reactive intermediates can alter metabolic products through different chemical approaches such as disulfide formation, carbonylation and S-nitrotyrosylation [7]. High oxidative stress created due to inflammasome-driven inflammation also inhibits DNA repair machinery. Activated neutrophil-derived myeloperoxidase have been shown to inhibit nucleotide excision repair in human pulmonary epithelial cells [13]. Several studies suggest that chronic inflammation may initiate genomic instability in carcinogenesis. Microsatellite instability and loss of heterozygosity have been reported to subsequently transform ulcerative colitis to dysplasia or cancer [14]. Reduction of telomere repeats were seen in liver cells surrounding hepatocellular carcinoma [15].

Certain inflammasome proteins like NLR family pyrin domain containing 3 (NLRP3) have been found to have distinct correlation with cancers. One study reported that activated hepatic stellate cells express NLRP3 inflammasome and mice lacking either NLRP3 or ASC (Apoptosis-associated speck-like protein containing C-terminal caspase-recruitment domain) component of inflammasome were protected against tetrachloride-induced liver damage [16]. Another study demonstrated that mice deficient in NLRP3 inflammasome components showed reduced production of IL-1β and IL-18 and subsequent reduced liver injury after acetaminophen treatment [17]. In methylcholanthrene-induced fibrosarcoma model, NLRP3 deficient mice displayed significantly reduced tumor incidence than wild type mice [18]. Carcinogenic role of NLRP3 was also identified in malignant mesothelioma where it contributed to acute IL-1β production and recruitment of immune cells [19]. The activation of inflammasome enhanced production of pro-inflammatory cytokines in mouse skin co-exposed to ultraviolet B irradiation and arsenic and led to epidermal hyperplasia [20]. Neutralization of inflammasomes and their products has pro-

found effect on controlling carcinogenesis. These studies indicate that inflammasome components are promising therapeutic targets and hold the potential to be biomarkers in malignancies. These evidences provide impetus for a comprehensive research aimed at translating cancer related inflammation into innovative therapeutic strategies.

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