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Compartmentalization Modules of Inflammatory Response are Centered on the Epithelial-Mesenchymal Transition of Transforming Cells in Carcinogenesis

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Abstract

The epithelial-mesenchymal transition (EMT) event in carcinogenesis is dependent on multiple operant pathways of master transcription as proposed for NF-kappaB and in terms of the initiated progression of malignant transformation. Inflammation is a primarily compartmentalized series of distinct and overlapping systems that induce and enhance multifocal operabilities within both the nucleus and cytoplasm by systems of enhancer/inhibitory modes of modulation of multi-gene transcription. In terms therefore of a compensatory system of response, carcinogenesis includes a series of steps in characterization of nuclear/cytoplasmic duality targeting ultimately the emergence of tumor cell invasiveness as the epithelial-mesenchymal transition. Emergence of such transition is hallmark for carcinogenesis within contexts of aberrant cell proliferation and anti-apoptosis as exerted by NF-kappaB proinflammation. NF-kB is the main transcription factor that regulates the expression of inflammation-related genes and is in turn influenced by autophagy; also autophagy interacts with inflammation in numerous disease states. It is relevant; in addition, that NF-kB participates in the release of inflammatory cytokines in patients with sepsis with pathogenic implications of sepsis in carcinogenesis.

Keywords: Carcinogenesis; Proinflammation, NF-kappaB; Compartmentalization

Introduction

The various effects of Nuclear-Factor kappaB (NF-kappaB) stimulation is closely related to the often-induced carcino-genesis of specific tumor-type and also specific cell-type involved [1,2]. Such measures reflect the master-transcriptional roles of NF-kappaB in a manner that emphasizes cell-type origin of the given tumor cell type, as ob-served especially in colitis-associated cancer, hepatocarcinoma, and other tumor types such as lymphomas. In terms of a compensatory system of responses, carcinogenesis includes a series of steps in characterization of nuclear/cytoplasmic duality targeting ultimately the emergence of tumor cell invasiveness as the epithelial-mesenchymal transition. It is in terms of activation and enhancement of nuclear localization of the site of action of NF-kappaB that operative carcinogenesis is a dually contrasting system of compartmentalization between nucleus and cytoplasmic localization.

Cytokines are especially implicated and CCL20 chemokine induces migration and invasiveness of human breast carci-noma cells in primary culture and activates NF-kappaB and MMP-9 via PKC-alpha [3].

Chronic Inflammation

The strong link between persistently chronic inflammation and especially infections is manifested in about 15% of the total tumor burden, but also operates also in such neoplastic types as castration-independent forms of prostatic epithelial tumors and also in aggressive examples of breast carcinomas that are estrogen-independent [4,5].

NF-kappaB/Twist plays a role in a signaling axis that involves tumor necrosis factor-alpha (TNF-alpha) following chronic exposure to transforming growth factor-beta (TGF-beta) and induces epithelial mesenchymal transition (EMT) and cancer stem cell-like attributes in HeLa cells [6]. Hence, the tumor-associated macrophages operate as activated NF-kappaB generators in the induction of tumor cells as paracrine system modules.

The release of chemically-mediated operators from neoplastic cells undergoing active necrosis activate such activated NF-kappaB in stimulating aberrant cell proliferation, anti-apoptosis, and the enhancement of invasive properties and metastases [7]. In particular, there is enhancement of the epithelial-mesenchymal transition phenomenon in a manner that promotes a whole spectrum of carcinogenesis with the development, progression and maintenance of angiogenesis and spread. Unregulated RPA2, a subunit of the heterotrimeric replication protein A, promotes NF-kappaB activation in breast cancer by suppressing menin, the multiple endocrine neoplasia type 1 tumor suppressor gene product, on NF-kappaB-regulated transcription [8].

Incremental Indices

Quantitative aspects in carcinogenic modulation are highly significant in mechanisms of carcinogenesis. Incremental indices operate in activation series of events as central roles of NF-kappaB to induce the production also of multiplicity and progressive size increase of individual tumor deposits. The specific products of such inflammatory response include Interleukin-1alpha and Interleukin-6 in particular that further enhance inflammatory severity and persistence.

Dimensions of cooperative systems such as chemically induced injury to colonic epithelium and injury to hepatocytes indicate an amplified response that attempts to control or replace injured cells. Vitamin D exerts preventive effects on inflammatory bowel disease by inducing anti-inflammation, immunoregulation and anti-cancer activities by suppressing EMT and cancer stem cells [9].

miR-127 enhances EMT and stem-like traits in lung cancer via a feed-forward regulatory loop involving the inflamma-tory signals NF-kB and tumor necrosis factor alpha-induced protein 3 [10].

The reparative/regenerative responses of injured hepatocytes are dynamically related closely to the ensuing pathways of hepatocarcinogenesis as well-defined by the hepatotoxin/carcinogen diethylnitrosamine. In the case of colitis-associated cancer, there is clear indication of inflammatory enhancement of carcinogenesis as induced experimentally by dextran sulfate sodium. Vanadium, a dietary micronutrient, appears to limit cell proliferation and oxidative DNA damage in liver, colon and also in mammary carcinogenesis.

Toll-like receptor (TLR) 2 promotes intrahepatic cholangiocarcinoma migration and invasion by inducing the expres-sion of epithelial-to-mesenchymal transition (EMT) markers, and up-regulates the pro inflammatory cytokines tumor necrosis factor (TNF)-alpha, Interleukin (IL)-6 and IL-1alpha concurrent with activation of NF-kappaB signaling [11].

Knockdown of SNAIL, a major EMT regulator in Kaposi's Sarcoma associated herpesvirus (KSHV) results in reduced expression of LANA (latency associated nuclear antigen); Par3 (partitioning-defective protein) enhances E-cadherin; also a SNAIL inhibitor diminishes NF-kappaB signaling through up-regulation of caspase3 in KSHV positive B-lymphoma cells in vitro [12].

The diverse and widespread gene targeting attributes of NF-kappaB are transference potentiality for systemic inflammation and the induction/enhancement of protective mechanisms of epithelial cells, in particular, as executed by the multi-gene targeting. In this manner, cell-protective actions by NF-kappaB allow for compensatory responses that in turn enhance the emergence of carcinogenetic pathways.

Gene Targeting

Multiple myeloma is a striking example related to stimulation of carcinogenesis by amplified NF-kappaB systems, with striking suppressive effects on carcinogenesis when inflammatory effects are inhibited, but other pathways are implicated as well, such as that mediated by NIK that is a member of the MAPK kinase kinase family.

Peroxiredoxin 1, a major antioxidant enzyme, promotes invasion and migration by regulating epithelial-to-mesenchymal transition during oral carcinogenesis and it also up-regulates the NF-kappaB pathway [13].

Both canonical and non-canonical NF-kappaB pathways are implicated in carcinogenesis in a manner that may involve mutual interactivities.

Inflammatory cytokines (like TNFalpha and IL-1), viruses, double-stranded RNA, and stresses that include both physi-cal and chemical agents, stimulate the canonical NF-kappaB. Key to regulation of NF-kappaB action is the Inhibitor of kappaB kinase (IKK) responsible for phosphorylation-induced degradation of the inhibiting IkB complex.

Inhibitors of Nf-Kappab

IKKbeta phosphorylation gradually increases in low to higher stage prostate cancer; also, it is significant that IKKbeta and hence NF-kappa B activation, increases in parallel with the expression of cell proliferation and survival markers (Ki-67 and Survivin) and epithelial-to-mesenchymal transition markers (Slug, Snail) as well as cancer stem cell-related transition factors (Nanog, Sox2, Oct-4) in human prostate cancer tissue micro-arrays [14].

Once IkB undergoes proteolysis, the nuclear localization signal of NF-kappaB dimers is exposed, with nuclear entry by NF-kappaB. Canonical NF-kappaB activation induces the innate immune system with the activation effects of IL-6, IL-1beta and GM-colony stimulating factor, chemokines such as IL-8, enzymes such as inducible NOS and COX-2, adhesion molecules and vascular endothelial growth factor itself. In such manner, activation of the innate immune system enhances the process of carcinogenesis.

The non-canonical NF-kappaB is activated by lymphotoxin (LT) beta receptor stimulation, BAFF (of the Tumor Necrosis Factor family) and CD40. With phosphorylation of p100 (NF-kappaB2) and stimulation of the processing of p52 that enters the nucleus bound to RelB to initiate gene transcription.

The alternative NF-kappaB pathway activates different components of the canonical NF-kappaB pathway, with en-hanced activation of BAFF, and of chemokines such as BLc, SLC, SDF-1, and ELC.

The reports of different actions of the NF-kappaB in carcinogenesis, in different experimental models, reflect the strong influence of specific cell-types in which activation, but not mutation, of components of the NF-kappaB is operative. Geminin overexpression-dependent recruitment and cross-talk with mesenchymal stem cells enhance aggressiveness and the EMT phenomenon in triple negative breast carcinomas [15]. In such manner, several upstream transcriptional and post-translational operants induce specific actions that modulate the transforming effects of inflammatory mediators within the NF-kappaB pathways.

Distinct Overlapping Pathways

The complex and often contradictory effects of such components of the NF-kappaB pathways include a vast range of targeted genes that are transcriptionally activated, as indicated by many of the most recent quoted publications concerning tumorigenesis. The performance modularity of NF-kappaB therefore includes in particular the enhancing action of Inhibitors of kappaB kinase in activating NF-kappaB through phosphorylation and acetylation in particular. Dimensions of operability have therefore directed therapeutic advances to downstream effectors of NF-kappaB in an attempt to modulate especially the inflammatory reactivities in the absence of component mutability.

NF-kappaB signaling plays essential roles in cisplatin-induced bladder cancer chemoresistance and cancer progression [16].

The alternative NF-kappaB pathway is implicated in lympho-organogenesis and in regulation of the humoral branch of the immune system and it, hence, operates as a distinct system that overlaps with the canonical NF-kappaB pathway. In such manner, distinct overlapping is a hallmark of the NF-kappaB pathways in a manner that includes dimerization of both homo-dimers and hetero-dimers in enhancing carcinogenesis.

The essential regulatory roles of inhibitors of NF-kappaB kinase are significant in terms of the creation of distinct mi-cro-environmental compartments within and external to the involved cells. Tissue inhibitor of metalloproteinase-4 is over expressed in several cancers and enriches the tumor progenitor cell population in cervical cancer cells and it modu-lates cell survival, cell proliferation, inflammation, and epithelial-mesenchymal transition signaling networks [17]. Lipocain-2 acts as a biomarker for cancers and it's over expression increases stemness and tumor metastasis by modu-lating NF-kappaB cellular signaling [18]. The production of such system overlapping is integrative in terms of the large number of transcriptional targets as exerted by activated NF-kappaB in the initiation, progression and maintenance of the carcinogenic phenotype. Such phenomenon is especially relevant to the epithelial-mesenchymal transition in subse-quently promoting invasiveness and metastatic spread of the malignant transformed cells.

EMT is a highly significant therapeutic target in oncology and serves as a central and potential mechanism in the con-trol of malignant transformation by NF-kB since it defines effects of transition to infiltrating and recurrent episodes in tumor progression due to inflammation accompanying tumorigenesis.

Concluding Remarks

Distinct overlapping pathways and components of NF-kappaB action allow for injury of targeted cells within systems of activation of multi-gene transcription in a manner that sharply distinguishes the onset and maintenance of a chronic inflammation that is often specifically of infectious origin. It is in terms of such activation and enhancement of nuclear localization of the site of action of NF-kappaB that operative carcinogenesis is a dually contrasting system of compartmentalization between nucleus and cytoplasmic localization.

In conclusive terms of operability, NF-kappaB is also a cytoplasmic operant in terms of the Inhibitors of NF-kappaB (IkB) and of IKK kinase. The vast array of enhancers and inhibitors of NF-kappaB relates to a master-gene transcription that modulates distinct profiles that in turn center on the epithelial-mesenchymal transition phenomenon. Strict compartmentalization events as a specifically modulatory role for the given and distinct cell type implicated in carcinogenesis would suffice to create and maintain carcinogenesis in terms of the epithelial-mesenchymal transition of that cell.

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