Inflammation in Cancer Development

Inflamación en el desarrollo del Cáncer

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Abstract: Inflammation plays an important role to the development of cancer and promotes all stages of tumorigenesis. Cancer cells, as well as inflammatory cells, carry out reciprocal interactions to form an inflammatory tumor microenvironment (TME). Cancer cells within the TME are highly able to change their phenotypic and functional characteristics. Here, we review the relationship between inflammation and infection in cancer origins, and the mechanisms whereby inflammation and infection drive tumor formation. We discuss how infection promotes tumorigenesis related to inflammatory processes typically found in autoimmune diseases, release of inflammatory mediators induced by tumors, inflammation induced by therapy in cancer, and stimuli for induction of inflammation during tumorigenesis, including spatiotemporal considerations. A better understanding of the fundamental rules of engagement that govern the molecular and cellular mechanisms of tumor-promoting inflammation will be essential for further development of cancer therapies.

Keywords: Cancer, tumor, inflammation, infection.

Resumen: La inflamación es imprescindible en el desarrollo del cáncer, pues participa en las etapas de la formación tumoral. Las células cancerosas y las células inflamatorias llevan a cabo interacciones reciprocas para formar un microambiente tumoral inflamatorio (TME). Dentro del TME, las células cancerosas son altamente capaces de cambiar sus características fenotípicas y funcionales. Razón por la que, nosotros revisamos la relación entre inflamación e infección en los orígenes del cáncer y los mecanismos por los cuales conducen a la formación tumoral. Discutimos cómo la infección promueve la tumorogénesis relacionada con los procesos inflamatorios que se encuentran típicamente en enfermedades autoinmunes, en la liberación de mediadores inflamatorios inducidos por el tumor, inflamación inducida terapéuticamente en el cáncer, y estímulos inflamatorios inductores de tumorogénesis, incluyendo las consideraciones espacio-temporales. Una mejor comprensión de las reglas fundamentales de participación que gobiernan los mecanismos moleculares y celulares de la inflamación que promueve tumorogénesis será la clave para mejorar las terapias contra el cáncer.

Palabras clave: Cáncer, formación tumoral, inflamación, infección.

INTRODUCTION

To elucidate the roles and the mechanisms of action of cancer and inflammation, it is important to understand how inflammation in cancer is induced and maintained in the first place. Approximately, 20% of all cancer cases are preceded by infection, chronic inflammation, or autoimmunity at the same tissue or organ site.[1,2] In this sense, cancer-induced inflammation exists long before tumor formation. Some examples include chronic hepatitis, inflammatory bowel disease (IBD), *Helicobacter*-induced gastritis which increase the risk liver cancer, colorectal cancer (CRC), and stomach cancer, respectively.[3] However, the action of systemic inflammation can take place even during the late stages of tumor development, as exemplified by bacterial-product-induced inflammation among other factors, which activate neutrophils and their extracellular trap formation function to promote breast cancer metastasis into the lungs.[4]

INFLAMMATION GENERATED BY THE TUMOR

The development of most cancers and individual tumors is not preceded by long-standing chronic inflammation. For example, IBD are predisposed to colitis-associated cancer (CAC), only around 2% of CRCs are preceded by intestinal inflammation. Nevertheless, some molecular studies describe the complexities of TME regarding cellular heterogeneity, and cell-to-cell differential transcriptomics that shown enhanced expression of distinct inflammatory cytokines and chemokines in primary tumors and metastatic lesions in inflammatory cell recruitment; in fact, the presence of certain cytokines, chemokines and myeloid cell subsets correlate with poor prognosis in CRC, as established in the "CRC immunoscore". In addition, neutralization or genetic inactivation approaches in pre-clinical animal models, demonstrates that inhibition of inflammatory responses in these seemingly "non-inflammatory" cancers stunts tumor growth and progression. The fact that cancers previously defined as "non-inflammatory" recruit immune cells and increase expression of inflammatory mediators to support tumor growth and reshape the TME to their benefit, has led to the term "tumor-elicited (or -associated) inflammation" (TEI). For that reason, inducers of TEI in microbial-induced tumors versus "sterile" tumors might be different. For example, in CRC early oncogene-induced deterioration of protective intestinal barrier at the site of tumor formation could lead to translocation of commensal bacteria and bacterial subproducts, which are recognized by tumor-associated myeloid cells to induce IL-23 production and IL-23-dependent TEI. In contrast, in tumors not associated with mucosal surfaces, the initial inflammatory trigger might come from metabolic alterations, sensing oncogenic transformation, hypoxia, and cell death.[5]

THERAPY AND INFLAMMATION IN CANCER

Although it is not present in intact tumors, another important type of inflammation is therapy-induced inflammation, which develops in response to various anti-cancer therapies, including chemo-and radiotherapy and, recently, immune infiltration caused by various biologic therapies or immunotherapies. Immune system activation in the tumor upon treatment is the cornerstone for current immunotherapies. This process certainly can be beneficial for stimulation of anti-tumor immune responses, which will collaborate with standard therapies. In some cases, release of damage-associated molecular patterns (DAMPs) such as ATP and High Mobility Group Box 1(HMGB1) from dying tumor cells can stimulate production of IL-1a and other immunostimulatory cytokines. This along with increased release of tumor neo-antigens might induce and sustain de novo anti-tumor T cell responses. However, the net outcome might not be uniform across tumor types or even individual tumors and will depend on how respective cytotoxic regimens or radiotherapies will affect activation and function of the cells of anti-cancer immunity.

Moreover, many tumors are deficient in apoptotic cell death and therefore cell death by necrosis might be more immunostimulatory. For example, necroptotic cell death of tumor cells might induce local and abscopal (the abscopal effect occurs when a tumor is treated with radiotherapy) anti-tumor immunity even in antigens between dying and residual tumor cells are not fully shared. Importantly, in many instances, partial destruction of tumors by therapies and release of dead cell material will also have immunosuppressive effects and will stimulate an inflammatory response overall resembling injury to normal tissue with subsequent wound healing and tissue repair. Here, recognition of dying tumor cells would stimulate the production of cytokines and growth factors, such as tumor necrosis factor (TNF), epidermal growth factor (EGF), IL-6, Wnt ligands, and others by the cells of the TME (such as myeloid cells and fibroblasts) and additional recruitment of these cells. These growth factors might serve as cell-extrinsic generally anti-cell death signals, which would decrease the efficiency of therapy being used. For example, paracrine EGF family ligand production, which can be elicited from macrophages or fibroblasts, is a major factor of therapy resistance in cancer. Other STAT3-activating cytokines such as IL-22, IL-11, and IL-6 were implicated into enforcement of stem cell phenotypes in cancer. With cancer stem cells being less proliferative and less metabolically active, they are less sensitive to many forms of chemo- and radiotherapy. Enhanced recruitment of myeloid cells and their release of the pyrimidine nucleotides confers resistance of pancreatic cancers to gemcitabine, exemplifying a non-immune, metabolic role of inflammatory cells in therapy resistance. Cytokines like IL-17 also can act directly on CRC cancer cells to provide them with resistance to a first-line anti-CRC therapy with 5-fluorouracil (5- FU) and inflammatory signaling target in remaining tumor cells is an important driver of therapy resistance. Yet, another probably underappreciated mechanism is the ability of chemotherapies to cause normal tissue damage, specifically in the intestine, translocation of inflammatory microbial products, and activation of systemic inflammation, which can further pro- mote tumors, as demonstrated for myelodysplastic syndrome and various metastatic cancers where microbial products accelerate metastatic growth. Altogether, therapy-induced inflammation develops only after treatment, but might play an essential role in determination of therapy efficacy or resistance to therapy. In this context, delineation of exact signals that induce inflammation during tumor development will undoubtedly help to fill in a broader picture how tumor evolution shapes the TME. [6,7]

STIMULI OF INFLAMMATION DURING TUMORIGENESIS

Several mechanisms and stimuli have been associated with inflammatory responses and causes that induce tumorigenesis. One of the hallmarks of cancer is the loss of cell-intrinsic tumor suppressor functions. One of the most mutated tumor suppressor genes is Tp53, encoding for p53 protein which has multifaceted functions to regulate cellular homeostasis, and one of them is its transcriptional antagonism with nuclear factor-kB (NF-kB), a key positive regulator of inflammation. NF-kB activate signals that are always present within the tumor microenvironment and even in a normal tissue; in fact, loss of functional p53 results in increased expression of NF-kB dependent inflammatory genes.[7,8] In colorectal cancer, this inflammatory signal contributes to tumor progression and metastasis, including, the loss of tumor suppressors that can also inhibit proper DNA repair and accelerate DNA damage, which can trigger DNA-damage- induced inflammatory pathways. The activation of oncogenes for cancer development is mechanistically linked to the increased production of cytokines and chemokines and recruitment of myeloid cells, which are either directly tumor promoting or immune suppressive, such as the oncogenic signaling K-Ras that regulates the expression of C-X-C motif chemokine ligand 3 (CXCL3), a key chemokine for myeloid cell recruitment. Other example is K-Ras activation that enhances production of cytokines and chemokines in a "senescence- associated secretory phenotype", such as IL-1a, IL-1b, C-C motif chemokine ligand 2 (CCL2), and CXCL1. The activation of K-Ras and c-Myc release CCL9, IL-23, and other inflammatory mediators in pancreatic cancer, and overall, the mechanisms where oncogene activation leads to excessive production of inflammatory

cytokines and chemokines might be a unifying mechanism for how inflammation is triggered in many cancers. [7,9] Pathogen such as H. pylori, H. hepaticus, hepatitis C virus (HCV), hepatitis B virus (HBV), or human papilloma virus (HPV), are involved in tumor progression and development and promote distinct inflammatory responses. Those examples where recognition of cancer-inducing pathogens through "classical" receptors recognizing have conserved molecular patterns that would trigger innate inflammatory responses. Cyclic GMP-AMP synthase (cGAS), sensors like Toll-like receptor 2 (TLR2) and TLR4, stimulator of interferon genes (STING), among others are associated with inflammasomes, sense oncogenic bacteria and viruses. However, many cancers might be promoted by commensal microbiota, either by translocation and adherence of microbes to cancer cells or by the distant release of inflammation-activating microbial metabolites.[7] Pancreatic cancer is often associated with chronic pancreatitis, which might be sometimes associated with infection or its inflammation-activating microbial metabolites but even in mouse models is driven by microbial- induced Th17 responses. On the other hand, non-alcoholic steatohepatitis (NASH) and fibrosis, which underlie hepatocellular carcinoma (HCC) development are actively promoted by intestinal microbiota and their products, and recent studies highlight the role of lung microbiota in induction of inflammation and tumorigenesis.[7,10] Moreover, the best example of commensal microbiota influencing tumor growth and progression comes from colon cancer in which it leads to the deterioration of intestinal barrier, because hyperproliferating cells fail to properly differentiate and form protective tight and adherent junctions and well-developed mucus layer, isolating immune compartment from bacteria. In fact, spectrum antibiotic treatment or rendering mice germ free reduces inflammation and tumor growth, even in animal models where potential pathogens are absent. Significantly, diet-induced changes in the microbiome promote tumor progression by activating K-Ras mutations. In CRC, bacteria have been suggested to be preferentially associated with carcinomas and adenomas, including subspecies of *Escherichia coli*, *Bacteroides fragilis*, and *Fusobacterium nucleatum*. Their presence could be capable of direct interaction with the surface of the tumor, either because of special ligand-receptor mode of adhesion, ability to form biofilms and initiate the outgrowth of the consortia of invasive bacteria, or ability to induce low-grade inflammation, disrupting the barrier.[7,10] It is reasonable to expect that in any microbe-rich cancer sites the tumor progression will be mediated by the inflammation they modulate. However, the ability to evade cell death is a prominent hallmark of cancer because it is possible to distinguish who dies, when, and how. Cell death is not only important in the therapy-induced inflammation, but also limited cell death of untransformed cells adjacent to tumor seeds might also be essential for tumor growth, especially in liver and skin. In liver cancer, the release of IL-1a, IL-6 and other growth factors promotes survival and growth of neighboring mutated hepatocytes, which is important to initiate inflammatory responses and tumorigenesis.[11] In this sense, the type of cell death might be important, with apoptosis and autophagy being less inflammatory and necrosis and necroptosis resulting in release of DAMPs being more potent inflammatory inducers.[7,11]

CONCLUSION

The source and/or inducer of inflammation in cancer might be different, in which the induction of inflammation could be always tightly linked with the emergence of factors absolutely needed for the oncogenic process, such as alterations in oncogenes and tumor suppressors, infections for microbial-induced cancers.[7,11,12] However, additional challenges in the field are needed to translate findings in animal models to human cancers, which progress with great genetic variability, dietary habits, and commensal and pathogenic microbe and virus composition.[7,12] Ultimately, several basic principles and mechanisms of how inflammation promotes cancer and TME could elucidate the complexities that govern the molecular and cellular mechanisms of tumor-promoting inflammation.

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