CANCER CONUNDRUM

CANCER RELATED INFLAMMATION

Carcinogenesis is a multistep process wherein a number of events occur during the natural course of the disease. The biology of cancer can be described under the following stages - initiation, progression, migration and metastasis.[1]

To rationalize the complex interactions occurring during the course of this debilitating disease, six hallmarks of cancer have been constituted. These include:

- Sustaining proliferative signaling
- Evading Growth suppressors
- Resisting cell death
- Enabling replicative immortality
- Inducing angiogenesis
- Activating invasion and metastasis.

Research in the last few decades has led to a better comprehension of the process of carcinogenesis at the molecular level. Progress in conceptual clarity in the previous decade has led to the emergence of newer hallmarks, namely:

- Genetic instability
- Tumor promoting inflammation
- Deregulating cellular energetics
- Evading immune destruction.[2]

Based upon experimental and epidemiological studies, tumor promoting inflammation/cancer related inflammation has emerged as the VII hallmark of cancer.

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The term inflammation, derived from the Latin word "inflammatio," is a complex biological response to harmful stimuli. This bodily response is comprised of two stages - acute and chronic. Acute inflammation is the initial stage mediated though the activation of the innate branch of the immune system. It lasts for a short period of time and functions in warding off infections and in repairing tissue damage in the body. Also known as "therapeutic inflammation," it aids in tumor suppression by activating the innate anticancer tumor response.

If this inflammation does not resolve over time, the second stage of inflammation sets in. Prolonged chronic inflammation has the potential to predispose one to a host of chronic illnesses including cancer.[3]

The response of the body to a precancerous or a cancerous cell is not very dissimilar to the body's response to inflammation and wound healing.

The German pathologist Rudolph Virchow speculated the role of leucocytes in neoplasia and deduced a connection between inflammation and cancer as early as 1863. He remarked that "chronic irritation manifested by a chronic inflammation is a key promoter of cancer".[3,4] Recent years have shown a resurgence in the concept of cancer related inflammation. This age old concept is now gaining back popularity owing to enhanced understanding of the inflammatory

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microenvironment. There is surmounting evidence that cancer also being a chronic process is a result of dysregulation in the inflammatory (process)/reaction. Factors such as tobacco, stress, dietary agents, alcohol, infectious agents, irradiation and other environmental stimuli can activate these inflammatory pathways.[5]

Two pathways link cancer and chronic inflammation - the extrinsic and the intrinsic.

In the extrinsic pathway, a constant inflammatory state (preexisting inflammatory conditions) present even prior to malignant transformation facilitates the development of cancer. The triggers of this pathway include chronic infections, autoimmune disorders and inflammatory conditions of uncertain origin.

In the intrinsic pathway, genetic abnormalities acquired by the precancerous cells by activation of various classes of oncogenes affect the signaling pathways resulting in induced availability of proinflammatory mediators which guide the construction of an inflammatory microenvironment, promoting tumorigenesis.[6]

The key orchestrators at the confluence of the intrinsic and extrinsic pathways are mainly the transcription factors (TFs) and pro-inflammatory cytokines. They include:

- Transcription factors
- Reactive oxygen and nitrogen species
- Inflammatory cytokines and chemokines
- Prostaglandins
- Specific micro RNAs.[7]

The main mediators of cancer related inflammation, which play a role in modulating the tumor microenvironment can be categorized into:[1]

Cellular component

- Innate immune cells - Macrophages, neutrophils, mast cells, myeloid derived suppressor cells, dendritic cells, natural killer cells
- Adaptive immune cells - B and T lymphocytes - further divided into CD8+ cytotoxic cells and CD4+ cells, T-helper cells (Th1, Th2, Th17, Tregs)
- Stromal cells - Fibroblasts, endothelial cells, pericytes and other mesenchymal cells.

Transcription factors

- NFkB, AP-1, STAT3, HIFα

Inflammatory cytokines

- Interleukin (IL)-1, IL-6, IL-8, IL-10, IL-12, Il-17, Il-23
- TRAIL, tumor necrosis factor (TNF) α, TGFβ, EGFR, IFNγ, FasL[1]

Pro-inflammatory cytokines are not only secreted by the precancerous and cancerous cells, but also by the stromal cells, which assist in the formation of a "sustained inflammatory microenvironment" directly aiding in malignant progression

The tumor microenvironment has a great significance as it comprises of all the soluble factors, which allow the flow of information among the tumor, stromal cells and the extracellular matrix (ECM) establishing a positive feedback loop within the infl ammatory micro milieu.[8] It is now an established notion that chronic inflammation of a persisting nature is detrimental to precancerous cells. It can cause oncogenic transformation by following the chain of events.

Generation and maintenance of chronic inflammation in tumors

This may be achieved through the extrinsic and intrinsic pathways, by activation of oncogenes, gene amplification and inactivation of the tumor suppressor genes (TSGs) by the cells undergoing a transformation. This leads to the activation of TFs - NFkB, STAT3 HIFα in the tumor cells. The TFs induce the overexpression of "pro-inflammatory mediators" - cytokines, chemokines, prostaglandins, reactive oxygen species and nitrogen intermediates (RONS).

Inflammatory cells get recruited into the tumor stroma, which in turn secrete elevated levels of the pro-inflammatory mediators. The TFs, the immune/inflammatory mediators, stromal cells, their secretions and their interactions with the precancerous cells constitute the tumor microenvironment, which collectively promote tumorigenesis. They precipitate an increase in tumor growth and survival, cause evasion of apoptosis and accelerate the processes of angiogenesis, invasion and metastasis.

Mechanism of sustenance of the inflammatory microenvironment

The TFs activated in the tumor cells, inflammatory cells, and stromal cells lead to an increased availability of the pro-inflammatory mediators which results in a "sustained smouldering" of cancer related inflammatory microenvironment.

Secondly, the production of RONS lead to the formation of free radicals, which induce DNA and lipid damage causing further gene mutations resulting in the accumulation of advanced glycated end products (AGEs). These AGEs bind to their receptor RAGE leading to chronic inflammation induced NFkB activation at sites of tissue damage. This activated NFkB - overrides endogenous anti-inflammatory mechanisms finally resulting in sustained inflammation.[9]

DNA damage by the production of RONS have the ability to inactivate RB-1 gene leading to cell proliferation, can

cause DNA strand breaks, aberrant DNA crosslinking, DNA adducts (byproduct of lipid peroxidation) cause point mutations in TSGs which lead to genomic instability. The free radicals further cause reduced expression and enzymatic activity of DNA mismatch repair genes, increase in the release of methyl transferases causing global hyper methylation of the genome and promoter silencing of several TSGs.[7]

The tumor related inflammation effectuates progression of the tumor by bypassing the p53 checkpoint through the action of migration inhibitory factor, increased production of growth factors and survival factors through the influence of COX2, NOS and TNFα, which stimulate tumor cell proliferation and survival by acting in a paracrine and autocrine manner, inducing angiogenesis in a hypoxia dependent manner by production of vascular endothelial growth factor and angiopoietin, reducing necrosis and apoptosis, accelerating the invasive and metastatic properties of the tumor cells by increased production of matrix metalloproteinases and TNF which cause accumulation of the tumor cells at lymph nodes.

It also causes subversion of immunity by reducing the cell mediated immune response by the action of ILs resulting in reduced cytotoxicity and immune evasion and by cellular senescence of suppressor T-cells. Finally, these mediators also have been found to interfere with chemotherapy by conferring chemoresistance to the tumor cells.

MicroRNAs are small, noncoding RNAs that regulate the transcription of specific genes. They are emerging as regulatory molecules in inflammation related cancer. As they represent inflammatory gene signatures, they could be used as prognostic biomarkers.[4,7]

For the past many years, all efforts to combat cancer have concentrated on the destruction/inhibition of tumor cells. However, with the growing evidence of the influence of the tumor microenvironment on the stages of carcinogenesis, modulating the host microenvironment offers a promising : perspective. Cancer Related Inflammation (CRI) should be considered as a target for innovative therapeutic strategies. Proinflammatory cytokines and their regulatory TFsrepresent primary targets and ongoing studies in this direction justify continuing efforts, which will ultimately relate to targeted therapy.

The undeniable fact that inflammatory reactions also result in antitumorigenic activity should be harbored upon. This dual function of inflammatory cells and mediators is reflected by studies on correlations between the parameters of CRI and clinical behavior in various contexts. The challenge now is to identify the mechanisms triggering a "therapeutic" inflammatory response leading to tumor inhibition, at the same time neutralizing its pro-tumorigenic actions.[10]

CONCLUSION

Inflammation is a protective physiologic response involving inflammatory cells, immune cells, blood vessels and molecular mediators in order to eliminate the initial cause of cell injury; clear necrotic and damaged tissues and initiate tissue repair. It is now evident that inflammatory cells and the presence of an inflammatory micro milieu have powerful effects on tumor initiation and progression. Early on in the neoplastic process, these cells can act as highly effective tumor promoters, creating a conducive environment for tumor growth, facilitating genomic instability and promoting angiogenesis.

The inflammatory cells along with the chemokines and cytokines secreted by them influence the whole tumor, regulating its growth and proliferation, migration and differentiation of all cell types in the tumor microenvironment, including the neoplastic cells and the stromal cells. Yet, the tumor formation elicits a host response by recruiting inflammatory cells, which are antitumorigenic in function in order to suppress tumor development and growth.

The pro-tumorigenic actions of the inflammatory microenvironment include releasing growth and survival factors, promoting angiogenesis and lymphangiogenesis, inducing DNA damage, remodeling the ECM to facilitate invasion, coating tumor cells to make available receptors for disseminating cells through lymphatics and capillaries and evading host defense and tumor suppressive mechanisms. Although inflammatory responses should also be antitumorigenic, cancer patients are known to have defective immune and inflammatory responses. This may arise by two distinct tumor-mediated mechanisms: A failure to upregulate the anti-inflammatory cytokines, or subversion of the host immune response resulting from desensitization of receptors owing to high chemokine and cytokine concentrations which blunt systemic responses.

Thus, cancer associated inflammation is a double-edged sword. Most of the components of cancer promoting inflammation have a dual role in tumor development. They can either function as a pro- or anti-tumorigenic molecules and factors based upon their expression levels, abundance, duration and state of activation in the tumor microenvironment. Some of the mediators with a distinct are presented in Figure 1.

The challenge for the future is to normalize the inflammatory network to regain a normal host response overall by decreasing the high levels of tumor-promoting properties of the infiltrating cells, that is, the pro-inflammatory cytokines, while increasing their tumor-suppressing properties, through anti-inflammatory cytokines. Putting this into effect, in tumor progression, the antitumorigenic activities can be harnessed, while suppressing those that are conducive to tumor development.[11]

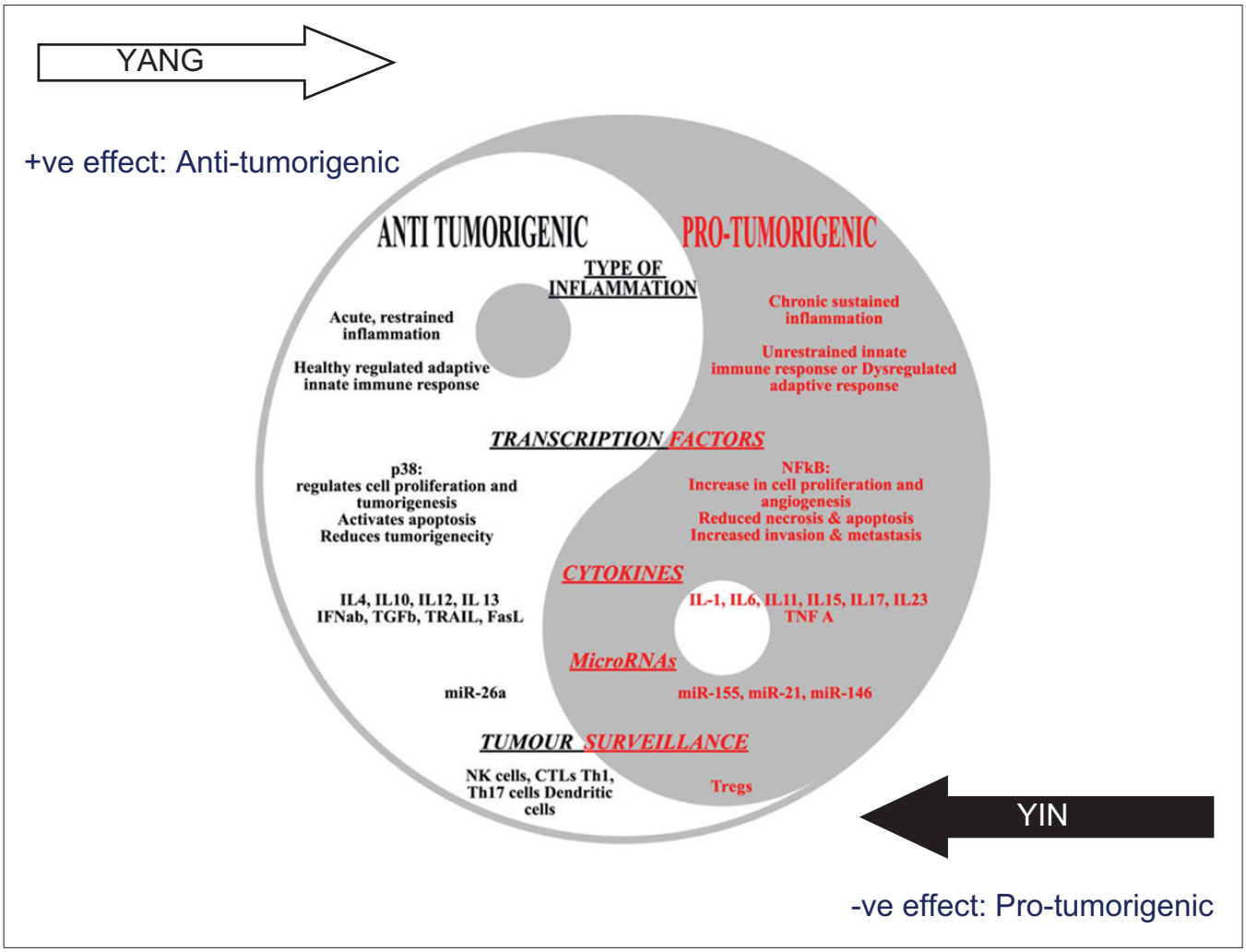

Figure 1: The pro- and anti-tumor effect of cancer associated inflammation depicted using the concept of Yin and Yang

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