The Role of Inflammation in Cancer and Systemic Lupus Erythematosus

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Inflammation is a tissue reaction against noxious foreign elements of the body, either internal or external elements. The reaction is characterized by infiltration of inflammatory cells to the injured tissue. The purpose is to destroy and eliminate foreign elements and restore injured tissue to its normal structure and function (wound healing).[1] In fact, inflammation sometime fails to eliminate the foreign elements. Therefore, it causes persistent inflammatory response in the body, which is known as chronic inflammation. It results in continuous endless apoptosis and wound healing process that may induce immunological chaos.[1]

As foreign elements, cancer cells also stimulate infiltration of inflammatory cells surrounding the tumor, especially the tumor associated macrophage (TAM). Macrophage plays a two-sided blade role. It has pro-inflammatory as well as anti-inflammatory properties depending on the activating signals. Cancer cells can alter the phenotype of macrophage so that it takes side on tumor progressivity and metastasis. Inflammatory cells including TAM release various pro-inflammatory cytokines and chemokines. The remarkable one is TNF-α, which has two roles, depending on the dose, it may play as a two-sided blade as well. High concentrations of TNF-α destroy tumor vasculature and induce tumor necrosis; while in low concentration, it has a role as tumor promoter. TNF-α induces the expression of COX2 that promotes angiogenesis. COX2 is an enzyme that catalyzes prostaglandin production (PGE2 and PGE1) from arachidonate acid. Prostaglandin plays role on inducing the production of certain pro-inflammatory cytokines, angiogenesis, cell proliferation and tumor invasion in chronic inflammation.[2]

TNF-α, IL-1β, and IFN-γ stimulate inflammatory cells producing free radicals in form of reactive oxygen intermedia (ROI) (e.g. hydroxyl radicals, superoxides, hydrogen peroxides, and single oxygen) and reactive nitrogen intermedia (RNI) (e.g. nitric oxide (NO), peroxynitrite and S-nitrosothiols) through activation of protein kinase signaling pathway. When ROI and RNI exceed their neutralizing system (antioxidant system), oxidative stress will occur. ROI and RNI are toxic substances that may react with proteins, carbohydrates and lipids, including DNA resulting in DNA and cell damage, which also stimulate inflammatory reaction. DNA damage itself leads to cessation or induction of transcription pathway, replication error and genomic instability.[2,3]

Pro-inflammatory cytokines such as IL-1 and TNF-α, hypoxia, ROI and genetic changes may activate NF-kB constitutively in cancer cells. The activation may contribute to anti-apoptosis effect, tumor cell growth and metastasis. Current evidences also indicate that key components of NF-kB system, including transduction molecules and its subunits play roles in modulating macrophage function and TAM activity.[4] In colorectal cancer, NF-kB has a role in progressivity through expressions of various

gene targets involved in cell proliferation (Cyclin D1), angiogenesis (VEGF, IL-8, COX2), and metastasis (MMP9).[5]

Incomplete inflammation, persistent inflammation, and failure of precise control on immune responses may impair microcellular environment, which subsequently induces changes of cancer-associated genes and modification of signaling protein of post-translational cells, which are involved in cell cycle, DNA repairing and apoptosis. In fact, mononuclear inflammatory cells are commonly present at the very early stage of tumor development, adjacent to areas of hyperplasia and atypia. These findings support the concept that mononuclear inflammatory cells are a steering force contributing to tumor initiation and/or initiation of tumor progression. Activated NF-kB factor is also one of the main links between inflammation and tumorigenesis and may be key to allowing malignant and pre-neoplastic cells to escape from apoptosis.[6] Such correlation of inflammatory process can be seen on large bowel disease (Crohn's disease and especially ulcerative colitis) and colorectal cancer and hepatitis B and C or alcoholic liver cirrhosis and hepatocarcinoma.

In SLE, autoantibody binds to body tissue itself by activating the complement cascades and induces cell lysis and or diminution of cells by phagocytic cells such as macrophages, neutrophil, CD4+ of self-reactive T helper cells, CD8+ of self-reactive cytolytic T cells, with a small number of NK cells, mast cells, and dendritic cells. Immune cells cause damage directly by killing the cells or indirectly by releasing cytotoxic cytokines, prostaglandin, RNI or ROI.[7] In harmony with cancer initiation, pro-inflammatory cytokines may also have role as the initiator of SLE development, which is an autoimmune disease, in addition to genetic mechanism. TNF and IL-1β are pro-inflammatory cytokines produced by nature and adaptive immune response. When the cytokines are injected in mice, there is higher incidence of autoimmune disease in genetically susceptible mice or tolerance break in genetically resistant mice. It indicates that resistant genetic factor can be developed into autoimmune disease due to infection or something that increases pro-inflammatory cytokines.[7] Another theory describes that development of autoimmune disease is caused by macrophages inability to destroy apoptotic cells.[8]

Not only on cancer and autoimmune disease, but chronic inflammation may also have roles in the formation and development of other chronic disease. At the development of atherosclerosis, there is an increased transcytosis of low-density lipoproteins (LDL), which form fatty streaks at the lumen of the vessel. Fatty materials contain lipoproteins that lose contact with antioxidant substances, producing oxidized LDL (oxLDL) and inducing a local inflammatory response. The oxidized LDL increase the expression of toll-like receptors (TLR) as well as the activity of NF-kB and concentration of monocyte chemoattractan protein-1 (MCP-1) and interleukin-8. Activation of circulating monocytes, along with an increased expression of adhesion molecules such as VCAM-1 and ICAM-1 mediated by endothelial dysfunction, increase their ability to infiltrate into vascular endothelium. Monocytes that infiltrate into the endothelium differentiate into macrophages, which are not capable in eliminating debris leading to accumulation of them on vascular walls.[9]

In addition to local changes, inflammation also causes systemic effects. If there is leukocyte infiltration at inflammatory sites, then systemic circulation reveals leukocytosis, lymphopenia, and neutrophilia.[10]

At first, Zahorec proposes neutrophil lymphocyte count ratio (NLR) as additional marker of infection in clinical practice at ICU. He found a good correlation between NLCR and disease severity as well as the outcome.[11,12] Later, NLCR has also been used as independent predictor factor of survival on various conditions from oncologic patients to patients with cardiovascular disease. In colorectal cancer, pre-operative univariate analysis demonstrates reduction on overall survival and cancer-specific survival in patients with NLR $\geq$5 compared to those with NLCR <5.[10] NLCR >5 is also a risk predictor on advanced-stage colorectal cancer progression, which has been treated with chemotherapy.[13] In cardiovascular diseases, Papa

et al through a multivariate analysis demonstrates that NLCR is an independent predictor of cardiac mortality (HR 8,13) together with CRP, cardiac ejection fraction, fasting blood glucose level, HDL and serum iron level (SI).[14]

At last, unrealized, inflammation is a two-sided blade, which one of them is prompt to jeopardize human life through its pleitrophic (dualism) of various involved components, starting from inflammatory cells (macrophages) to cytokine molecules (TNF-α, COX2, prostagladin, and NF-kB). However, chronic inflammation and its component bring benefit to medical practice since it acts as biomarkers which may indicate the presence of initiation, promotion and progression of the abovementioned diseases. Moreover, it may even become therapeutical target, predictors of prognosis and survival as well as treatment outcomes (drug resistance). Anti-inflammatory drugs (aspirin, indometasin, diclofenac, naproxen, dexamethasone, etc), immunosuppressive agents (such as cyclosporine) and (such as carboplatin and gemcitabine) may inhibit NF-kB activity. Resistance to chemotherapy and radiotherapy may occur due to NF-kB activation; therefore, it may become a biomarker for predicting resistance.[15]

With regard to the role of inflammation, this edition of Indonesian Journal of Internal Medicine is featuring two Indonesian manuscripts showing the role of COX2 and NF-kB on colorectal cancer and the role of neutrophil lymphocyte count ratio as activity marker of SLE. The role of COX2 and NF-kB on colorectal cancer in Indonesia turns out to be important considering the rapidly increased incidence of colorectal cancer in Asia which is consistent with transition in developing countries as well as the important role of ethnicity in the development of colorectal cancer. Neutrophil lymphocyte count ratio as the marker of SLE activity is a new horizon in determining disease activity correlated to MAX-Sledai based on the role of chronic inflammation on autoimmune disease. Although it has not been statistically significant, but it still becomes a guideline for investigators in searching activity marker, which is inexpensive, simple and feasible in Indonesia.

REFERENCES

1. Khatami M. Inflammation, aging, and cancer: friend or foe? In: Khatami M, ed. Inflammation, chronic diseases, and cancer-cell and molecular biology, immunology, and clinical bases. Croatia: InTech; 2012. p. 3-30.
2. Keibel A, Singh V, Sharma MC. Inflmmation, microenvironment, and the immune system in cancer progression. Curr Pharm Design. 2009;15:1949-55.
3. Federico A, Morgillo F, Tuccillo C, Ciardiello F, Loguercio C. Chronic inflammation and oxidative stress in human carcinogenesis. Int Journal J Cancer. 2007;121(11):2381-6.
4. Sica A. Role of tumour-associated macrophages in cancer related inflammation. Experiment Oncol. 2010; 32(3):153-8.
5. Wang S, Liu Z, Wang L, Zhang. NF-kB signaling pathway, inflammation and colorectal cancer. Cell Mol Immunol. 2009;6 (5):327-34.
6. Eiro N, Vizoso. Inflammation and cancer. World J Gastrointestinal Surg. 2012;4(3):62-72
7. Fairweather D. Autoimmune disease: mechanisms. Encyclopedia of Life Science; 2007:1-6.
8. Aprahamian T. Autoimmunity, atherosclerosis and apoptotic cell clearance. In: Khatami M, ed. Inflammation, chronic disease, and cancer cell and molecular biology, immunology and clinical bases. Croatia: In Tech; 2012. p.3-30.
9. Gonzales-Chavez A, Elizondo-Argueta S, Satierrez-Reyes G, Leon-Pedroza J. Patophysiological implications between chronic inflammation and the development of diabetes and obesity. Circulation. 2011; 79:190-97.
10. Tavares-Murta BM, Murta EFC. Open Cancer J. 2008; 2:53-8.
11. Zahorec R. Ratio of neutrophil to lymphocyte counts-rapid and simple parameter of systemic inflammation and stress in critically ill. Bratish Lek Listy. 2001;102 (1):5-14.
12. de Jager CPC, van Wijk PTL, Mathoera RB, de Jongl-Leuvenink J, van der pol T, Wever PC. Lymphocytopenia and neutrophil-lymphocyte count ratio predict bacteremia better than conventiona infection markers in emergency care unit. Crit Care. 2010;14:2-8.
13. Chua W, Charles KA, Baracos VEM, Clarke SJ. Neutrophyl/lymphocyte ratio predicts chemotherapy outcomes in patients with advance colorectal cancer. Brit J Cancer. 2011;104:1288-95.
14. Celik T, Bugan B. Letter to editor. White blood cell count and stable coronary artery disease. The role of neutrophil to lymphocyte ratio. Cardiol J. 2011;18 (6):720.
15. Aggarwal BB, Sethi G, Nair A, Ichikawa H. Nuclear Factor-kB a holy grail in cancer prevention and therapy. Current Signal Transduction Therapy. 2006;1:25-52..