# Auto-Immune Diseases and Cancer

*Arya Sugathan, **Sreekumar T, ***Smitha Mohan, ****Shaji K, *****Athulya

**Abstract**

Cancer and Auto- immune diseases have attributed relationship between various domains of the immune system. Both diseases develop due to the dysfunction of immune response. It shares a common origin with opposing pathology. Cancer often develops because of the suppression of immune system and failure to attack on the defective cells and allowing cell division. In auto immunity, hyper action of immune response that mistakenly attacks the healthy cells. Even these each immune responsible disease works in opposite direction, they have some similar microenvironment, especially hypoxia, macrophages, neutrophils and their interactions. Understanding the specific actions of immune response to the cancers and auto immunity may help to avoid the contradiction in between and to improve the therapeutic strategies.

**Keywords**

Cancer, auto-immune disease, hypoxia, macrophages, neutrophils.

## Introduction

The immune system is the body's biological defense mechanism to prevent infection and to protect the host to eliminate toxic substances from the body[1]. The immune system can be divided into innate immunity and adaptive immunity. Innate immunity is the initial responds of the immunity system to invading pathogens. That include phagocytes (macrophages and monocytes), neutrophils, dendric cells, mast cells, eosinophils and others. But it has less effective than adaptive immunity[2]. Adaptive immunity is the second line of defense and it is specific to the pathogens with long lasting responds. It includes T cells (cytotoxic T cells), T helper cells (Th1)- produces IFN-ɤ, IL-2 and (Th2)- produces IL-4, IL-5, IL-13 and other subtypes include- Th-17, IL-17A, IL-17F, IL-22 and T regulatory cells (Treg). Other lymphocytes of the adaptive immune system are B cells, it responds specifically to an antigen.

Immunity system can also be categorized into pro- inflammatory (Th1, Th2, M1 and pro-inflammatory mediators) and anti-inflammatory (dominated by Th2 cells, M2 and anti-inflammatory cytokines)[3]. When comes to cancer and auto-immune diseases, both diseases develop due to the dysfunction of immune response. In cancer, the tumor cells promote anti-inflammatory response to suppress the anti-tumoral immunity because it cannot survive in inflammation and the tumors got well differentiated. In contrast, in auto-immune disease, the hyperactivity of immune system against the host cells, that are misrecognized as antigen, leading to tissue damage. Even these both diseases have the opposite function it has some similarities in their microenvironment.

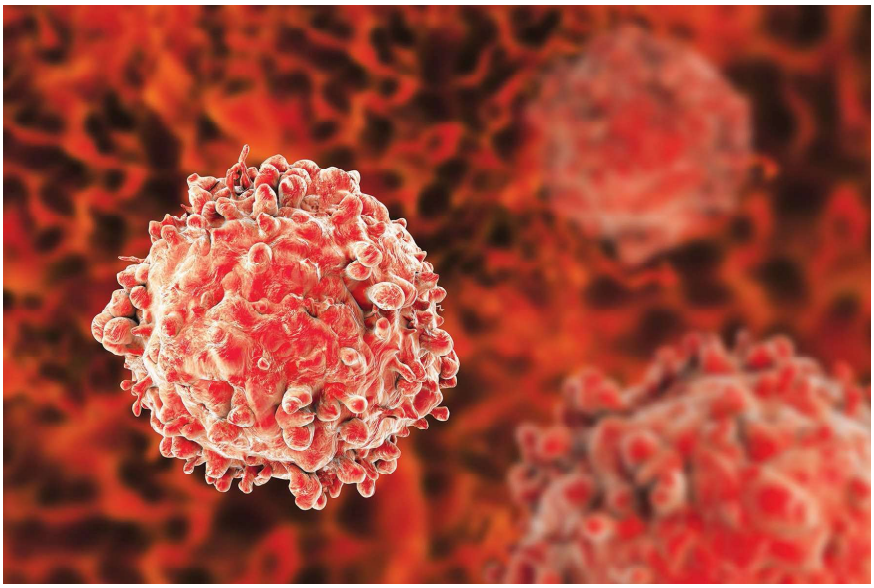
## The microenvironment in cancer and auto-immune disase

The tumor environment is composed of endothelial cells, fibroblast, perivascular cells and inflammatory cells which regulate angiogenesis, desmoplasia, lymphomagenesis and inflammation respectively[4].

### Hypoxic Microenvironment

All inflamed tissue suffer from low oxygen tension termed hypoxia. Hypoxia results the induction of hypoxia-inducible factor (HIF), which regulate glucose metabolism, angiogenesis, cell proliferation and tissue remodeling. Upregulation of HIF-1α induce angiogenesis and shift to glycogenesis. This anerobic glycolysis increases lactate level which leads to cellular acidosis. When the

*Second year PG Scholar in Shalyatantra, **HOD & Professor of Shalyatantra, ***Professor of Shalyatantra, **** Assistant Professor of Shalyatantra, ***** Assistant Professor of Shalyatantra, PNNM Ayurveda Medical College, Cheruthuruthy, Thrissur District, Kerala.



lipid peroxidation increases the cell membrane gets damaged. So the membrane permeability increases causing recruitment of leukocytes and trigger inflammation.

In cancer, uncontrolled proliferation of tumor cell increases the tumor mass, when it increases to a diameter of 2-3 mm the blood vessels and nutrients cannot reach up to its site hence result hypoxia. It induces the activation of HIF and regulate angiogenesis and glycolysis then later enhances anerobic metabolism. As a result of these mechanism lactic acid increases and transported out of the tumor. Where it exposed to macrophages and contributes to its polarization and generate M2- phenotype. So, the Tumor Associated Macrophages (TAMs) produces the hallmarks of tumorigenesis.

In auto-immune disease, low oxygen tension were reported and upregulate HIF-1α, it mediate an angiogenesis and leads to the infiltration of leucocytes and drives the secretion of proangiogenic factors. So the mechanism of hypoxia and angiogenesis are common in both cancer and auto-immune diseases, which is necessary for both cell survival and disease progression.

## Macrophages

Macrophages are important cells of the immune system, formed through the differentiation of monocytes. When these monocytes migrate into tissue where it differentiates into macrophages and perform multiple functions include balancing homeostasis, wound healing, tissue repairs etc. by the secretion of inflammatory or anti-inflammatory mediators. All these functions cannot be performed simultaneously so they divide into many subtypes according to the cell's microenvironment[5]. Macrophages can be categorized into either M1 or M2 subtype. M1 macrophages produce high level of proinflammatory cytokines and that eradicates tumor cells and promotes Th1 responds[6]. M2-macrophages which produce anti-inflammatory mediators. It further distinguishes into M2a, M2b, M2c where M2a are fibrotic, M2b are immune regulators and produce IL-1β, IL-6, and TNFα, and M2c are anti-inflammatory and are involved in tissue repair and remodeling6.

Tumor Associated Macrophages (TAM) contribute to cancer through two mechanisms.

1. Activation of cell-stimulating growth factor
2. Suppression of anti-tumoral immunity[7].

That means if the response is pro-inflammatory it turns against the tumor cells and if the responds is anti-inflammatory it promotes tumor growth. In auto-immune diseases the role of macrophages is not well defined, it demands more researches.

## Neutrophils

Neutrophils are a type of white blood cells, making up 50-70% of whole WBC. It act as the first line of defense against the different pathological conditions and helps to heal the damaged cells. It constitutes multiple function according to the condition by releasing effector molecules and cytokines. In cancer and auto-immune disease, neutrophils play a vibrant role with the subsets of N1, N2, or HDL, LDL and LDGs or CD177 respectively.

Neutrophils in cancer, also known as tumor associated neutrophils (TANs). TANs have two sub divisions N1- tumor suppressing and N2- tumor promoting phenotype. Based on density TANs can be divided into HDNs and LDNs. N1 subtype mostly act at the early stage of tumor, it have anti-tumoral function with the proinflammatory action by releasing cytokines, such as IL-12, TNF-α etc., which facilitates activation of CD8+ T cells[8]. N2 neutrophils are immunosuppressive and tumor promoting activity mainly acting during the period of tumor progression. It stimulates angiogenesis, invasion and metastasis via various factors like, reactive oxygen species (ROS), reactive nitrogen species (RNS)[9] etc.

Studies shown that TGF-β and type 1 interferons involved in polarization of neutrophils that is in the presents of TGF-β, neutrophil produce N2 phenotype and whereas the blockade TGF-β facilitates N1 phenotype[10]. Interferon 1 also involved in the synthesis of N1 and N2 with the presents and impaired signals respectively.

Based on density gradient of neutrophils it is divided into high-density neutrophils (HDN)

and low-density neutrophils (LDN). LDN is again divided into mature and immature based on shape of nucleus. HDN functions similar to N1 neutrophils- act as immunostimulatory with pro inflammatory reactors. LDN resembles N2 neutrophils. Interestingly, some HDN can converted into LDN by TGF-β[11]. Neutrophils plays a major role in the pathogenesis of auto-immune disease like RA, SLE etc. Auto-immune diseases develops, when the body fails to recognize the foreign and self-antigens. It plays a central role in the production of aberrant immune responds and results into the development of tissue damage. And neutrophils are believed to be a major factor for the generalization of auto-antibodies. More researches are needed to enroll the action of neutrophils in auto-immune diseases.

## Ayurvedic perspectives

The modern understanding of immunity fits in the broad concept of vyadhikshamatva in ayurveda. Factors which contribute for vyadhiksamatva are normal dosa, equilibrium state of dhatu, normal agni, srotas etc. or factor which supports the equilibrium state of all physiological parameters[12]. According to Susrutha, samprapthi of arbuda is 'the dosas having vitiated in any part of the body especially kapha dosa and afflicting the mamsa and produce swelling. It is round with mild pain, big in size, deep rooted[13]. When the kapha is in normal state it called 'bala' as well as 'ojas' but in abnormal state it is then called 'mala'and 'roga'. Which means the factors responsible for shopa will trigger the bala of the individual along with the derangements of dosa and agni thus realizing the relation between inflammation and neoplasia[14].

## Discussion

An autoimmune disease is a condition in which the immune system mistakenly attacks the body. In many auto immune diseases, there is an increased risk of cancer compared to the general population. The connection between these two is dynamic and bidirectional. Chronic inflammation and tissue damage induced by auto immunity adversely affect the ability to clear oncogenic infection. Similarly, after a diagnosis of deadly deceases like cancer and its immunosuppressive therapy may develop clinical manifestations of auto immunity.

## Conclusion

Cancer and auto immune disease are two clinically opposing diseases but it shows some similarities in broad pathogenesis. For example, hypoxia and angiogenesis. The production of different molecules in the microenvironment of each diseases shows at least two subsets of molecules, either immune-stimulatory/ suppressive or pro/anti-inflammatory. In short cancer and auto immune diseases are arising from immune system dysfunction. And the nidana of both diseases are similar that causes sopha and imbalance of dosa dhatu agni etc. Approximating the pathogenesis of cancer and auto-immune diseases can contribute the plan ayurvedic care intermentions in the clinical setup.


**References:**

1. Chaplin DD. Overview of the immune response. J Allergy Clin Immunol. 2010;125(2 Suppl 2):S3-S23. doi:10.1016/j.jaci.2009.12.980.
2. Childs CE, Calder PC, Miles EA. Diet and Immune Function. Nutrients. 2019 Aug 16;11(8):1933. doi: 10.3390/nu11081933. PMID: 31426423; PMCID: PMC6723551.
3. Rahat MA, Shakya J. Parallel Aspects of the Microenvironment in Cancer and Autoimmune Disease. Mediators Inflamm. 2016;2016:4375120. doi: 10.1155/2016/4375120. Epub 2016 Feb 22. PMID: 26997761; PMCID: PMC4779817.
4. Finger EC, Giaccia AJ. Hypoxia, inflammation, and the tumor microenvironment in metastatic disease. Cancer Metastasis Rev. 2010 Jun;29(2):285-93. doi: 10.1007/s10555-010-9224-5. PMID: 20393783; PMCID: PMC4012531.
5. R. D. Stout and J. Suttles, "Functional plasticity of macrophages: reversible adaptation to changing microenvironments," Journal of Leukocyte Biology, vol. 76, no. 3, pp. 509–513, 2004.
6. Mills C.D. M1 and M2 Macrophages: Oracles of Health and Diseases. Crit Rev. Immunol.2012;32:463-488
7. Justin K Messex et al. Signaling of macrophages that contours the tumor microenvironment for promoting cancer development cells.2006;9(4):919
8. Coffelt SB, Wellenstein MD, de Visser KE. Neutrophils in cancer: neutral no more. Nat Rev Cancer (2016) 16:431–46. doi: 10.1038/nrc.2016.52
9. Powell DR, Huttenlocher A. Neutrophils in the tumor microenvironment. Trends Immunol. (2016) 37:41–52. doi: 10.1016/j.it.2015.11.008
10. Fridlender ZG, Sun J, Kim S, Kapoor V, Cheng G, Ling L, et al. Polarization of tumor-associated neutrophil phenotype by TGF-â: "N1" versus "N2" TAN. Cancer Cell (2009) 16:183–94. doi: 10.1016/j.ccr.2009.06.017
11. Sagiv Jitka Y, Michaeli J, Assi S, Mishalian I, Kisos H, Levy L, et al. Phenotypic diversity and plasticity in circulating neutrophil subpopulations in cancer. Cell Rep.2015:(10)562–73. doi: 10.1016/j.celrep.2014.12.039
12. Dr P. S Byadgi.Ayurvediya vikriti vijnana and Roga vijnana. Chukambha publications.2007;1(3):294
13. Prof. K.R. Srikantha Murthy.Susrutha samhitha. Chaukhambha Orientalia.2010. nidana sthana; vol-1 (102):534
14. Department of salyatantra.National seminar and workshop on arbuda.Ayurvedic management of Arbuda.dept of salyatantra.govt Ayurveda college tripunithara.2011;jan 15-16