Circulating Immune Complexes: Epimutation and Tumorigenesis

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Circulating Immune Complex (CIC) is the binding of the antigen with its corresponding antibody by electrostatic van der Waal force, to form an interlock. The formation of immune complexes (IC), due to the interaction of foreign substances (including microbial agents) with specific antibodies, is a physiological process which constitutes an essential part of man's normal immune defence mechanisms against the foreign substances and are usually eliminated by the mononuclear phagocytes system (MPS) without development of pathological changes [1]. Thus, circulating immune complexes is considered here as a cumulative product of immune responses due to environmental influences capable inducing epimutation and tumorigenesis. Immune Complex (IC) formation is considered an environmentally (exogenous) and systemically (endogenous) sourced epimutagen in which case pathogen associated molecular pattern (PAMP) and damage associated molecular pattern (DAMP) respectively, can serve as immunological risk factor capable of mediating the immune complex formation. These immune complexes may persist, thus creating enabling environment for obstruction of the normal homeostasis, epigenetic cell alteration and subsequently leading to tumorigenesis or carcinogenesis. In any normal immune response, the half-life of CIC is transitory in nature. Continued presence of CIC over extended periods, however, may be a cause of consequence of some pathological condition or infection [2,3] and may include cancer.

Environmental, as used by cancer researchers, means any cause that is not inherited genetically. Thus, the term environment refers not only to air, water, and soil but also to substances and conditions at home and at the workplace, including diet, smoking, alcohol, drugs, exposure to chemicals, sunlight, ionizing radiation, electromagnetic fields, infectious agents, etc. Lifestyle, economic and behavioral factors are all aspects of our environment” [4]. Based on this, it is opined here that the end point of exogenous molecules such as proteins, carbohydrate, lipo-proteins, lipo-polysaccharides which could emanate from microbial agents and their toxins, food, air and water, as well as from chemicals toxins and pesticides residues, is centred on immune complex formation. In the same vein, the end point of endogenous molecules such as damaged associated molecular pattern (DAMP) is also centred on immune complex formation. Thus, the pathological effects these exogenous and endogenous molecules may have in the body are chronically based on immune complex formation and retention. The role of infection/inflammation in the initiation and progression of cancer has been an area of intense scientific interest and is usually considered from the perspective that persistent inflammation in the context of chronic infection or tissue injury might promote cell transformation through DNA damage or that tumor cells

produce proinflammatory factors that encourages chronic inflammation and tumor growth [5,6].

So much importance has been attached to the role of immunological responses in tumour development. This calls for a focus on immunologically inducible pathways mediated and activated by the presence of certain antigenic components in circulation and thus suspected to lead to tumour development and progression. This would be likely where enabling environmental factors seem to favour retention of antigens in circulation. While the discovery that viruses can cause tumours in animals was traced back to 1st century [7], the implication of microbial and parasitic diseases in the causation of human cancers has been demonstrated [7]. The burden of infection-associated cancers depends on a variety of factors. Although incidence of cancer is higher in developed world than in developing countries, it is important to note that presentation of cancer in developing worlds seem to be marked with poor prognosis.

Insights into the molecular and cellular mechanisms underlying cancer development have revealed that immune cells functionally regulate epithelial cancer development and progression [8]. Moreover, accumulated clinical and experimental data indicate that the outcome of an immune response towards an evolving breast neoplasm is largely determined by the type of immune response produced by the host. Acute tumour-directed immune responses involving cytotoxic T lymphocytes appear to protect against tumour development, whereas immune responses involving chronic activation of humoral immunity, infiltration by T helper lymphocyte type 2 (Th2) cells, and protumor-polarized innate inflammatory cells result in the promotion of tumor development and disease progression [5].

Tremendous progress have been made over the last decades at understanding the biology of tumours, however the mechanism for growth and progression of tumours with acquisition of invasive and metastatic phenotypes and therapeutic resistance are still not fully understood [9,10]. It is crucial to understand the aetiology of these sporadic cancers in order to develop adequate therapeutic or preventive strategies against the devastating disease. The recent appreciation of the influence of microbiota on human health and disease begs the question of whether microbes play a role in sporadic breast tumours of unknown etiology or not.

The binding of antigens to their corresponding antibodies tagged immune complexes have been shown to trigger a lot of immunological responses and have been associated with many pathological conditions. Formation of immune complexes and the activation of complement were associated with the appearance of a wide variety of tissue pathology in experimental animals, which cleared as the immune complexes were removed from the circulation. These pathologic effects included vasculitis, carditis, glomerulonephritis, as well as rheumatologic and dermatologic manifestations of disease [11]. Circulating immune complexes are physiologically removed by the Mononuclear Phagocytic System (MPS), however their relative persistence in health and known pathological conditions such as cancer in environmentally polluted areas, calls for need for their assessment. Under normal conditions, immune complexes (IC) are usually eliminated in the system and are not detectable in the system. Research has shown that detectable levels of IC are found in chronic or persistent exposure to foreign substances or ongoing infection [12]. The ability of CICs to classically and continuously activate immune responses, thus making it a potential immunological ligand that can progress tumorigenesis has been neglected over-time and as such deserves attention. Circulating immune complexes (CICs) are now viewed as regulators of both cellular and humoral immune responses by virtue of their capacities to interact with antigen receptor bearing lymphocytes and sub-population of T and B cells as well as with macrophages and neutrophils having FC receptors [13]. Circulation of immune complexes can stir up complement activation, opsonization, phagocytosis, activation of immune cells (macrophages, neutrophils) and subsequent release of cytokines, chemokines and activation of protease pathways [1]. Moreover, immune complexes deposited intravascularly can directly engage circulating leukocytes thus releasing inflammatory mediators (cytokines and prostanoids) capable of activating the endothelium and their ability to recruit more cells [1]. Additionally, research has shown that by circulation, circulating immune complexes can deposit...
in tissues of organs and induce complement activation and subsequent release of chemotactic factors attracting phagocytes to the site of deposition. Based on these, it is proposed that circulation of immune complexes is a potent signal ligands capable of initiating the signal transduction and thus continued to induce secretion of pro-inflammatory molecules (cytokines), expression of inflammatory genes. This process could induce release of reactive oxygen species (due to activated immune cellular activities), and DNA oxidative damage markers. Moreover, the overall homeostatic obstruction due to immune system overhaul could perturb the epigenetic mechanism, leading to epigenetic cell alteration such as DNA methylation shift, histone modification, chromatin remodelling and over expression of micro RNA or non coding RNA. Alteration of normal homeostasis by persistent induced chronic inflammation, during the sensitive period of epigenesis or reprogramming, could enhance clearing or abnormal retention of the epigenetic marks. Thus if such epigenomic alteration persists in a tumour suppressor gene, expression of such gene could be altered and the cell may lose the normal pattern of interpretation of DNA instructions (altering the normal ON or OFF position of the tumour suppressor gene) as well as suppressing apoptosis, therefore enabling certain cell growth or proliferation. It has been well demonstrated that the decrease in global DNA methylation (demethylation) or increase in CPG island methylation (hypermethylation) is one of the most important characteristics of cancer [14].

**BIBLIOGRAPHY**


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