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Cytokines

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INTRODUCTION:-

Cytokines affect nearly every biological process in the human body. These include embryonic development, disease pathogenesis, non-specific response to infection, antigenic response, cognitive function changes and the progression of degenerative process of aging. Stem cell differentiaton, vaccine efficacy and allograft rejection are the certain functions exerted by the cytokine. This study mainly concentrates on cytokine biology and how these non-structural proteins affected the fields of inflammation and immunology. The hallmark of a cytokine is pleiotropism. The term "cytokine" encompasses a host of molecules like interferons, the interleukins, the chemokine family, mesenchymal growth factors, the tumor necrosis factor family and adipokines.

EVOLUTION OF CYTOKINES:-

The term cytokine is derived from a combination of two Greek words - "cyto" refers to cell and "kinos" refers to the cell movement. Cytokines are basically the cell signalling molecules that aid cell to cell communication in immune responses and stimulate the movement of cells towards sites of inflammation, infection and trauma.[1]

Cytokines originated from the earliest forms as intracellular molecules before the appearance of receptors and signalling molecules. Star-fish and *Drosophilia* showed cytokine like activities, where they displayed an important role in host defense and repair. [2] A survival mechanism was demonstrated in poikilothermic lizards wherein a cytokine-mediated rise in body temperature was observed. Some cytokines function as transcription receptors as well as extracellular ligands for specific receptors which evolved later.

In the human body, the biology of cytokine comes from the host production of "pus". In the ancient world, the writers documented the exudates containing pus and the presence of fever, local swelling and and pain. Pus was visible and later studied in the laboratory.[3] The field had its earliest advance with interest in soluble factors as they were then called as products of white blood cells which were studied in the mid-1940's. The cytokines are best defined as soluble factors produced by one cell that acts on another cell. Cytokines can also function as integral membrane proteins and some of them are never released from the cell. With the exception of the red blood cell, every cell in the body can produce as well as respond to a cytokine.

Cytokines exist in peptide, protein and glycoprotein forms. The cytokines are a large family of molecules that are classified in various different ways due to an absence of a unified classification system. Cytokines circulate in picomolar concentrations and may increase in magnitude almost a thousand-fold in response to an infection or inflammation. Cytokines have a many sources for their production, with almost all the cells that have a nucleus capable of producing interleukin 1, interleukin 6, and tumor necrosis factor alpha, particularly endothelial cells, epithelial cells and resident macrophages.[4] Another factor that contributes to the difficulty in distinguishing cytokines from hormones is that cytokines can exert systemic as well as local effects.

PIONEERING DAYS OF CYTOKINES:-

The factors responsible for establishing a link between a disease and the response of the host were the soluble factors released from the neutrophils from the peritoneal cavity of the rabbits. Fever, resistance to viral infections, elevated white blood cell count, synthesis of acute phase proteins, death of cancer cells and migration of inflammatory cells are the various biological properties exhibited by these soluble factors.[7] Until the mid-1970's, soluble factors as regulators of lymphocyte functions were not studied. Igal Gery and Byron Waksman gave the first description of 'lymphocyte activating factor' and later as T-cell growth factor. A paradigm developed that a disease process induces the production of these cytokines from cells and it is the property of these "factors" that account for the manifestations of the disease. Innate immune response is nothing more than a cytokine storm to infection or to cell damage triggered by Toll-like receptors. Non-specific nature is the hallmark of innate immunity as the response occurs repeatedly, regardless of triggering event.

NOMENCLATURE OF CYTOKINES:-

Interleukin was basically the term used to describe cytokines that were assumed by researchers to be the targeting leukocytes. Interleukins did not only target leukocytes and the term is now mainly used to name and number new cytokines as they are discovered.[5]

Lymphokine production represents a general biologic phenomenon which may play a role in various aspects of host defense. Such mediator substances should be called as 'cytokines'. Lymphokines represent a restricted set of cytokines made by one class of cells called as lymphocytes.

TIMELINE IN THE EVOLUTION OF CYTOKINES:-

- 1926 -Zinsser & Tamiya found permeability factors in supernatants of tuberculin sensitized guinea pig cells exposed to tuberculoprotein.
- 1932 -Rich & Lewis showed migration of neutrophils & macrophages in cultures of tuberculin-sensitized tissues was inhibited by antigen.
- 1957 -Isaacs and Lindenmann -Type I interferon.

- 1966 -David, Bloom & Bennett used the capillary tube technique to show that antigens could stimulate sensitized lymphocytes in cultures to produce macrophage migration inhibitory factor (MIF).
- 1968 -Ruddle & Waksman identified leukotriene.
  - 1969 -Dumonde suggested the word "lymphokine" for these mediators.
  - "Monokines" were defined when monocytes were cultured.
- 1974 -Cohen et al., proposed the term "cytokines".

PRO INFLAMMATORY CYTOKINES:-

Pro-inflammatory cytokines proved to be beneficial for the the bactericidal capacity of phagocytes, recruit additional innate cell populations to sites of infection, induce dendritic cell maturation and direct the subsequent specific immune response to the invading microbes.[8]

Three pro inflammatory cytokines, interleukin-1 ,IL-6, and tumour necrosis factor-α, appear to have a central role in tissue destruction. They are secreted by a variety of cell types comprising monocytes, macrophages, dendritic cells, epithelial cells, keratinocytes and fibroblasts.

IL-1α is a regulator of intracellular events and a local inflammatory mediator, while Il-1β is primarily an extracellular protein released from cells. IL-1 stimulates the proliferation of keratinocytes, fibroblasts and endothelial cells of the tissues. Therefore IL-1 is a critical component in the homeostasis of tissues and its unrestricted production may lead to tissue damage.

IL-6 is produced locally in the inflamed tissues following cellular activation by bacterial lipopolysaccharide or other cytokines such as IL-1β or TNF- α.

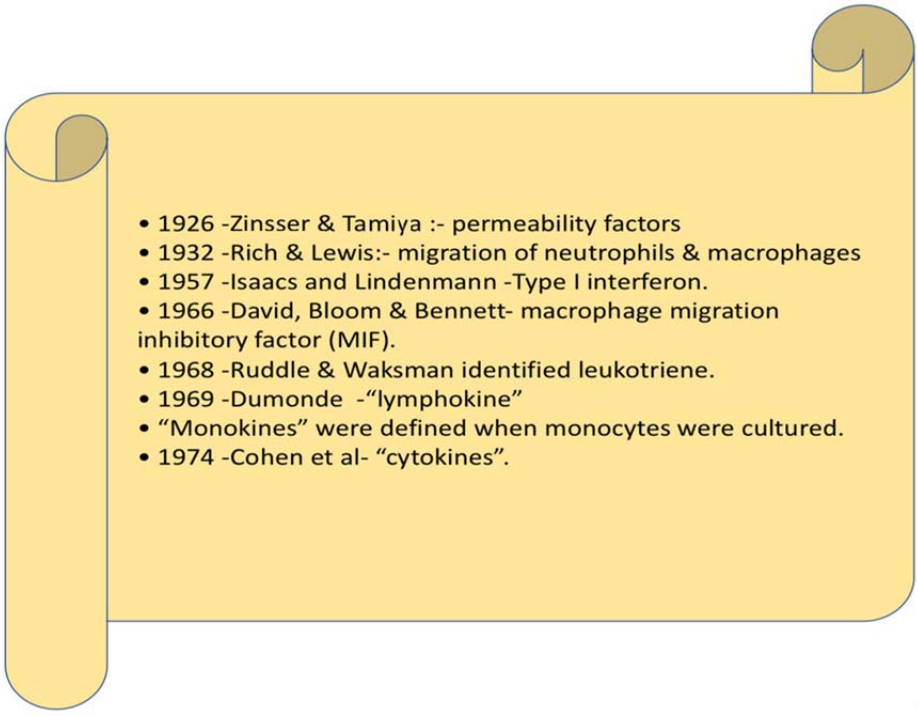
Tumour necrosis factor- α is a pro-inflammatory cytokine that possesses a wide range of immunoregulatory functions.[9] It has the potential to stimulate the production of secondary mediators, including chemokines or cyclooxygenase products, which amplifies the degree of inflammation.

ANTI-INFLAMMATORY CYTOKINES:-

The anti-inflammatory cytokines are basically a series of immunoregulatory molecules that control the proinflammatory cytokine response. Major anti-inflammatory cytokines include interleukin-1 receptor antagonist, IL-4, IL-6, IL-10, IL-11, and IL-13. Interleukin-4 promotes Th2 lymphocyte development and causes inhibition of LPS-induced proinflammatory cytokine synthesis. Interleukin-6 causes inhibition of TNF and IL-1 production by macrophages. IL-10 results in inhibition of monocyte/macrophage and neutrophil cytokine production and inhibition of TH1-type lymphocyte responses.[10] IL-11 inhibits proinflammatory cytokines by monocyte/macrophages and promotes Th2 lymphocyte response. Interleukin-13 shares homology with IL-4 and shares IL-4 receptor and attenuation of monocyte/macrophage function.

CONCLUSION:-

Cytokines are the key modulators of a wide range of bodily functions. Several cytokines exhibit some redundancy in function and share overlapping properties along with their cell surface receptors. Being mediators of inflammation and immune response, these molecules have been targeted as therapeutics in various diseases. So, a better understanding of the history and biological aspect of these cytokines can facilitate the development of agents for improved modulation of inflammatory response for the treatment of autoimmune, infectious and neoplastic diseases.



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