Human immuno-suppression therapy in SARS-CoV-2

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Abstract
The innate and adaptive immune systems are two interdependent bandwidths of immunity advanced during evolution process. Protection from foreign pathogens is the central theme of defense mechanism. Components of the immune system are well laid orchestra for keeping the immune system on alert. Robust host defense and cytokine storms are the key areas requiring attention with finality with introduction of IL-6 inhibitors or small molecules.

Keywords: Immune system, T cells and B cells, Innate, Adaptive, Cytokine, Lymphatic system.

Relevance of mechanics of immunology become so very important in this pandemic of SARS- COV-2 responsible for Novel COVID-19. It explains the exaggerated response of the defense mechanism of the human body to defend the attack of the virus, the initial robust host defense and the second cytokine storm.

Protection of an organism of any species from foreign pathogens is inherent for reasons of survival of the fittest. Human species has inbuilt protection mechanism provided during the evolution process. Highly sophisticated two wings are constituted by interdependent "innate" and "adaptive" immune systems.

Robust host defense mechanisms are reflected by "cellular" and "humoral" immunity. Any aberration in their balance results into immune mediated chronic inflammation.

"Innate" immune responses are immediate and in rapid succession eliminating the 'invaders' by phagocytosis. Activation of this innate system follows recognition of molecular pattern expressed by the invader prokaryotic primitive invertebrate organism like bacteria. Molecular patterns are not expressed by eukaryotic cells present in the host tissue.

Lipopolysaccharides present in bacteria and double stranded RNA present in retroviruses are recognized by receptors of the host like in invertebrates focusing the innate system only.

This activation of the innate immune system by recognition of microbial constituents is an ingenious and simple mechanism to discriminate between self and non-self, which initiates rapid and strong response to the invading micro-organism.

Priming of Activation of Innate Immune Cells
On initial encounter with microorganisms, activation of innate immune cells gets primed. This priming during subsequent en- counters gets deliberated into non-specific and limited response. Importantly, a second-encounter by the same microbe will not result in a more specific response.

Initial 800 million years of evolution, another arm of immune system evolved during subsequent 480 million years as "adaptive system" along with interdependent innate immunity in higher species starting from fish, amphibians, reptiles, birds and mammals etc.

The adaptive immune system is relatively slow as regards to the invader on first encounter. Specific cells of the adaptive system are the T cells. They take time to get activated in the draining lymph nodes, where these cells first divide and then only become functional.

Compared to the innate system, the adaptive system recognize pathogens in highly specific fashion. They have the ability to form much stronger immunological memory. During repeat infection, they respond rapidly like innate system.

The resultant memory T and B cells form the basis of vaccination success, like in small pox.

The immune system achieves equilibrium between favoring host defense against foreign pathogens and protecting host tissues from collateral damage.

Tilt in this delicate balance becomes pathological. In immune deficiency, emergence of serious infection or occasionally a neo- plastic disease can be promoted. Conversely, with sustained and unbridled immune

response or badly adapted immune system can trigger allergic, inflammatory and autoimmune disease.

Cellular Players in Immune Harmony

The immune chronology is performed in the human body consisting of

1. Circulatory Pathway
2. Lymphatic Pathway
3. Lymphatic organs

Eye and testicles are specialized organs apart from the followings playing a role, more as dedicated targets in reflecting the disease locations, thus helping in identification.

1. Skin
2. Joints
3. Kidney

Central lymphoid organs are the conductors of immune mechanism, which are located as follows:

1. Thymus
2. Bone marrow, where the cells (T & B Cells) of the immune system get to train themselves.

Secondary central lymphoid organs-spleen, lymph nodes and mucus membrane are seats of various remedial inflammatory locations.

The players of the innate immune system are cells like polymorphs, leucocytes, monocytes/macrophages, dendritic cells, and natural killer cells (NK).

The components of the adaptive immune system principally, T and B cells, require to be master operators.

C D - Various surface molecules differentiate the cells of the immune system from each other. These molecules are termed - cluster of differentiation. Each immune cell has specific C D molecules.

The key components are substances synthesized to establish communication between cells. High affinity receptors receive the communication and become capable of interacting with specific ligands such as soluble molecules - cytokines and chemokines exercising different functions.

Bone marrow and Lymph Node/Spleen

Progenitor generating centre of the immune system is the bone marrow. Most immune cells originate here and migrate to the peripheral blood, lymphoid organs and thymus. Pluripotent precursor cells in the bone marrow produce myeloid progenitor cells and subsequently polymorphonuclears monocytes, macrophages and dendritic cells.

The lymphoid progenitor cells in bone marrow produce T and B cells and a specific cell, the N K Cells.

Lymph Node/Spleen Peripheral Lymphoid Organs

These are places for lodgement of dendritic cells already loaded with captured antigens facilitating T and B cell activation.

Role of Lymphoid Tissues with Mucus Membrane

Mucus membrane is crucial for host defense, as they are spread to constitute a massive surface area of tissue in lungs and intestine allowing direct contact with the environment.

The lymphocyte infiltrate lodged therein is called, MALT (Mucosa Associated Lymphoid Tissue) either as bronchial or gut associated. Tonsil and appendix are such enriched areas, too.

This MALT system functions like the lymph node and spleen allowing special interactions between Antigen Presenting Cells (dendritic cells) and lymphocytes. This MALT system has a unique characteristic that it may appear and disappear depending on the environmental stimuli.

It is now accepted that this lymphoid neogenesis is seen in synovium and its persistence is seen in rheumatoid arthritis and other chronic immune pathological conditions.

Immune regulation and generation of specific effector defense responses are coordinated in the lymphoid organs. Cell contact dependant pathways are though, less well defend, also exist.

Immune regulation is based on interaction, activation and expansion of specific subsets of T and B cells.

Aberrations of Immunity

Dysregulation of immune response results into the pathogenicity of multiple immune-mediated inflammatory diseases. The two extremes of this dysregulation are having either deficiency or with overactive (inappropriately persistent) immune responses.

Immune Deficiencies

Inherited immune deficiencies are x-linked, monogenic and recessive. Each one is a specific 0clinical disease

entity guided by genetic anomaly and resultant interplay of cellular or molecular immunity.

Acquired Immune Deficiencies

Acquired immune deficiencies, AIDS is caused by a virus, which destroys T cells, dendritic cells and macrophages. It gains access through high affinity interactions with cells surface receptors like CD4 co-receptor and chemokine receptors. Use of glucocorticoid and or the cell depleting biological treatment further augments the acquired immune deficiencies.

Auto-inflammatory Syndromes

These are inherited diseases with persistent, systemic and chronic inflammatory responses. They are monogenic, arising through poorly understood aberrations of inflammatory signaling pathways. Two groups of such diseases are:

1. Certain forms of Crohn's disease and other related granu- lomatous diseases. Excess production of uric acid with precipitation to form urate crystals also might stimu- late similar intracellular pathways leading to inflammatory syndrome, i.e. GOUT. In adult stills disease or PFAPA syndrome (Periodic fever, Aphthous stomatitis, Pharyngitis, Adenitis) the mechanism remains unknown but may turn out to be inherited polygenic disorder.
2. Recurrent hereditary fevers, comprising of familiar Mediterranean fever, cold urticaria and CINCA (chronic infantile neurological cutaneous and articular syndrome), are considered to be inherited disturbances of the innate immune response.

Auto-immune Diseases

Rheumatoid arthritis/Type I diabetes are most probably caused by response of the cells of the adaptive immune system i.e. T and B cells, to tissues of the host. Autoantibodies are found, which is specific for the particular disease. Invariably, HLA system has an association, indicating the involvement of T cells. Cure of an autoimmune disease is often difficult because-

1. B and T cells form memory cells
2. Autoimmune response is directed against an antigen expressed by a person's own body. Exact aetiology of autoimmune diseases evade an answer, but they definitely involve multiple mechanisms.

Lymphoproliferative Disease

Dysregulation of the basic mechanisms contemplate apoptosis, as well as, chronic stimulation arising through persistent infection i.e. Epstein-Barr virus infection:

1. Sjogren's syndrome - this autoimmune disease apart from those, with increased incidence of B cell lymphoma is considered to be because of linkage between chronic immune stimulation and persistent antigenic stimulation.
2. ALPS and Follicular Lymphoma-the "malignant" lymphocytes proliferate, since the immune system, no longer eliminates them.

SARS-CoV-2

SARS-CoV-2, mass infection across the globe has resulted into declaration of pandemic by WHO. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), previously known by the provisional name 2019 novel coronavirus (2019-nCoV) is a positive-sense single-stranded RNA virus.

SARS-CoV-2 has close genetic similarity to bat coronavirus, suggesting its bat-borne emergence. An intermediate animal reservoir such as a pangolin is also thought to be involved in its introduction to humans.

The basic reproduction number of the virus has been estimated to be between 1.4 and 3.9. The reproduction number may be higher in densely populated conditions such as those found on cruise ships and aircrafts.

Human to human transmission of the virus has been confirmed all over the globe.

This enveloped single stranded RNA virus enters the host cell by binding to ACE2 (human angiotensin converting enzyme II) receptor.

The virus uses human ACE2 molecule as its entry receptor in lungs, this is considered a HALLMARK OF TRANSMISSIBILITY. This receptor binding domain is located in the amino-terminal regions. Amino acids of the SARS-COVID protein are directly involved in binding to ACE2.

It has Ability to use Human ACE2

ACE has a role in both innate and adaptive immune responses by modulating macrophage and neutrophil function. These effects are further magnified with over expressed ACE production. ACE is a zinc - dependant dicarboxypeptidase. It originally plays a major part in blood pressure regulation by converting angiotensin I to angiotensin II.

Neutrophils with over expressing ACE have an increased production of superoxide, increasing their ability to kill bacteria. Expression levels of ACE are particularly high in lungs, kidney, placenta etc.

ACE is Primarily Located in Cell Membrane

Macrophages have a crucial role as antigen presenting cells by interacting with T cells in adaptive response.

Effect of ACE Inhibitors on Immune Response

Extensive evidence in experimental animals indicates that inhibition of ACE typically suppresses the autoimmune process. In humans, there is little information on its effectiveness in treating rheumatoid arthritis, though one small cohort study suggests a positive effect of ACE inhibition in 66% patients. Hydroxychloroquine is touted to be effective in prevention and therapeutics of CoVID by inhibiting the ACE2 and other related mechanisms. HCQ, thus does not allow entry of the virus in the lung parenchyma, the target organ. Ivermectin, an anti-parasitic "wonder drug" (Penicillin and Aspirin-two other wonder drugs) has been confirmed to perish the virus within 48 hours in Australian laboratory in in-vitro studies. A prophylactic Ivermectin tablet can prove to be anti-parasitic as well but additionally it is recommended to liberally use ivermectin shampoo for its viricidal action in the hairs and neck region after doffing off the PPE equipment. Similar viricidal effect has been proved beyond doubt by the anaesthetic ether because it dissolves the outer fat layer of the virus. For this reason, drops of ether soaked in a spoonful of sugar, put on the tongue to be sucked with the mouth closed, is hypothasised to kill the virus in very early stage, when the virus is still lodged in the throat /respiratory tract. A patient requiring intubation for being connected to a ventilator, can be an accurate time for giving this inhalation ether anaesthesia in sub-optimal dose, which is effective in eliminating the virus from the lungs, and the circulation. Ether at this stage is also bound to improve oxygenation and ventilation because of vascular dilatation at the alveolar-vascular exchange level. Close circuit ether anaesthesia though, has become obsolete, but is the demand of the CoVID era to be brought back as the first line anaesthetic tool for any desirable anaesthesia required in an otherwise fit patient undergoing surgery with no lever comorbidities. Exposure to aerosol generation can be minimized by bypassing it, but these aerosols are likely to be sterile without any viral presence because of viricidal action. Cross infection to the anaesthesia team and other operation theatre occupants becomes negligible. With the existing work station, an ether evaporator can still be connected to facilitate safe anaesthesia administration.

Additional human studies can only lead to better mechanistic understanding of how exactly ACE effects the immune response. This is a key area of interest and holds great promise for novel immune-suppressive therapies including the role of IL-6 inhibitor (Tocilizumab 400 mg single dose intravenous) specially during second cytokine storm in later stages of coVID-2 especially following acute crisis resulting into low oxygen saturation during the culminating into deterioration of the patients general condition including damaged to lungs, kidneys, heart and brain. IL-6 over production is held responsible for this second cytokine storm. This storm is also the end result in a post-operative or post-traumatic period in a CoVID patient. This second cytokine storm is responsible for sudden deterioration and death in a convalescing CoVID patient. For reasons of cost and availability, the targeted synthetic small molecule Baricitinib (not Tafacitinib), it has not extensively been used but, comparable results with Tocilizumab should be ruled than exception in this stage of second cytokine storm.

Immunomodulation by IL-6 inhibitor administered at an early recognition of deterioration in the systemic disease process will save many lives.

Summary

Receptors in the host in invertebrates recognize the lipopolycecride present in the invading organism specially a bacteria or a virus operated by the innate defense system. Discrimination between self and non-self is a simple mechanism activating the innate immune system as a strong response to the invading microorganism. Priming of the innate immune cells on initial encounter and its known specific limited deliberation on subsequent encounters by the same microm does not result in a more specific response. Comparatively the adaptive system recognizes pathogens in highly specific fashion with stronger memory resultant T and B cells form the basis of vaccination success like in small pox. SARS-CoVID-2, a chimeric virus borne out of bat and pangolin has been a challenge to the mankind and the effect of ACE inhibitors on immune system can only lead to vector mechanistic understanding and is a

key area of interest. Voluminous release of Interleukin -6 draws attention during second cytokine storm with definite role of IL-6 inhibitor in this stage of COVID disease.

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Conflict of Interest
None.

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