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Opinion: Immunology of Mononuclear Phagocyte System in Pulmonary Pathotype of COVID-19

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Abstract

Mononuclear Phagocyte System MPS has an essential role in all stages of human SARS-COV-2 pulmonary infections. The objective of the present opinion paper was to through a light on the forefront achievements on the immunology of MPS in COVID-19. Single cell mRNA sequencing, single nucleus RNA sequencing, PCR, transcriptomics, flow cytometery, histo and gross pathology were the main assays tempted for assessments through an in-vitro, ex-vivo and in-vivo experimental settings. Monocyte, macrophage, alveolar macrophage, dendritic cells via an increment or decrement shift in number or function could probe the disease severity. MPS cells are either primer infected and lead to serial cellular events ended with severity. Or the epithelial cells found in the micro-environmental continuum with the APS were infected leading to MPS cell infection followed by cell-cell cross-talks, positive loop feedback mechanisms with T lymphocyte and/or MPS cells interferon axis functions. The overall immune response patterns of the lung in severe COVID-19 were; hyper-inflammation, immune impairment, hypoxia and severity terminated with death if not managed at earliest. An immune six point severity index was proposed as a diagnostic battery to be of use in an advance immunology laboratory was suggested. Molecular immune concept of circuit was briefed. MPS immune functions in pulmonary COVID-19 hold the position of double sward beneficial in some functional aspects and deleterious in others.

Keywords: *Alveolar, Asymptomatic, Cytometery, Dendritic cell, Flow, Infection, Macrophages, Monocyte*

Introduction

Mononuclear phagocyte system MPS take part in the functions of the human immune system both in health and disease. As a system is composed of circulating monocyte and tissue resident forms, the tissue resident forms got different names in different tissue microenvironment as; Glial in brain, alveolar in lungs, Kupffer in liver, osteoclast in bone, dendritic in spleen and other lymph glands and blood stream and Langerhans in skin. Some of which undergoes phase transition as that of glial cells in central nervous system. MPS performed immune functions both in the natural (innate) and adaptive immune responses. In other word they take part in immune cross-roads functions. In general MPS interplay immune functions in viral diseases and have special immune potentials in COVID-19. In health, MPS performed; phagocytosis, antigen presentation, shaping the adaptive immune responses, production of cytokines and chemokines. While in disease state MPS played a role in the infectious inflammatory processes and in immune tissue injuries due to an excessive cytokine production insitue in the affected tissue microenvironment [1-3]. In the present opinion tempts were made to review the immunology of mononuclear phagocyte cell system in pulmonary COVID-19.

Cellular Immunology of MPS

MPS cells originated from the pluripotent stem cells in bone marrow in human adults. From the stem cells, lympho-myeloid progenitor cell line was developed which then differentiated to pro-monoblast, mono-blast, pro-monocyte then to monocyte in blood stream. From blood stream migrate to tissue compartments. During such migration they undergo morphologic and functional changes that fits to the target tissue compartment or organ while migration within blood vessels would not accompanied by morphologic, functional and/or mitogenic changes.

MPS cells are of large sizes and have multiple secondary lysozymes. They are characterized by active endoplasmic reticulum and active Golgi apparatus which means have both active biosynthetic pathways and active secretions with an evident acclimatization to their microenvironment. In lungs MPS express oxidative metabolism, their half-life were ranged between 60 to90 days in various organ/systems. During the inflammatory stimuli, therein there are increments in the in their development in bone marrow and disseminated to various tissues through blood stream. On surface of MPCS cells there are numbers of markers like: MHCI, MHCII, C1, C2, FC, CD11, CD18, CD13, CD16, CD17, CD31, and IA. The biophysical characteristics of MPS are; stimulated by bacterial lipo-polysachaaride LPS and mitogenic lectins, adhere to glass, recognize the antigens by TLR receptor. They secrete; hydrolytic enzymes, enzyme inhibitors, cytokines, fat derived factors, complement components, and mirobicidal materials. When activated lymphocyte produce both of; macrophage inhibitory factor MIF it affects inhibition in spread of macrophages and macrophage stimulating factors which stimulate them for

pinocytosis, phagocytosis, and induce the appearance of immune associated antigen Ia and assist in antigen presentation. MPS own specialized mechanisms for recognition of different inflammatory stimuli. If the stimulus is microbe, they will evolve number of killing mechanisms. They evolve three highly efficient recognition and clearing mechanisms of immune complexes through phagocytosis. The presence of MPS in continuum of inflammatory responses they indicated either sub-acute or chronic inflammatory state. MPS cells act as; second line defender of human and mammalian body, antigen processing, antigen presentation, cytokine production and recognition of inflammatory responses [1-3].

Cell Molecular Immunology

There are varieties of natural immune protein that have the ability to recognize and detect human infection. These proteins are either soluble or structural entities like; soluble lysosome, complement components or complement receptors. The recognition process is through pattern recognition on the surface of the microbes. Among these receptors are the Toll-like receptor, the TLRs which are proteins of collectin nature that have the ability to recognize certain molecular patterns on the microbial surface. Such recognition molecules are forming strong features of natural (innate) immunity. TLRs are considered as a part of normal immune physiology. In the structural sense TLRs are forming a family of trans-membrane proteins that belongs to a class of animal lectins known as collectin proteins. TLR family is composed of more than ten different receptors. Most of the human and mammalian body tissues express at least one type of TLR. Though all TLRs are expressed onto; macrophages, dendritic cells, mast cells and B cells. TLRs interplayed an array of immune functions like; microbial sensors, cell signaling activators, enhancers for the expression of both; inflammatory and immune response genes, cross-linking of pattern-recognition molecules on the surface of microbe with TLRs act as danger signal to increase the microbicidal activity of phagocytic macrophages and allow them to activate T cells. TLRs made an important link between innate and adaptive immune responses. On TLRs activation, macrophage co-stimulatory molecules will converts macrophage phagocytes into antigen presenting macrophages which able to activate T cells [4-7].

Immunology of MPS in Human Virus Infections

The invading mammalian and human viruses when gain foot-hold in their respective hosts. They are recognized via their surface pattern recognition molecules PRM by the surface TLRs of MPS in blood stream and tissue resident. PRM cross-linked TLRs then virus pinocytosed, or through macro-pinocytosis and/or receptor mediated endocytosis in to the cell interior, Nikitina et al. [2018] the cross-link lead to transform of pinocytosed cell into antigen presenting cells. The processed virus peptides conjugated with MHC molecule and migrate out on the surface of MPS. The antigen presenting MPS will either activate naïve T cell to be Th2 triggering naïve b lymphocytes to grow, proliferate and expand as an effector antibody producing and memory B cells. Or activate naïve T cells to Th1 cells triggering T cells to be effector CD8+ cytotoxic T cells, CD4 T cells and memory T cells. The burden of virus load can be eradicated by the action of cytotoxic T cells or neutralized by the antiviral antibody and/or cleared by the direct action of interferons. The presence of molecular mimicking viral epitope with host tissue cells may initiate through the action of autoantibodies or auto-reactive cells immune tissue injuries terminated by autoimmune diseases. Excessive cytokine production by T cells or MPS also lead to inflammatory and immune responses with consequences of immune tissue injuries. The possible occurrence of viral immunosuppressive epitopes will trigger a state of infectious immunosuppressive conditions [6-9].

Immunology of MPS in SARS-COV-2 Infections

The circulating and tissue resident MPS cells, the monocyte and tissue macrophages participate in all stages of SARS-COV-2 human infection. They contribute to: (i) innate immune reactions (ii) shaping adaptive immune reactions, (iii) comorbidity predisposing to clinical infections, (iv) virus resistance, (v) virus dissemination, (vi) the host factors that determine disease severity, (vii) induction of immune tissue injury, (viii) recovery and (ix) sequalae (Table 1) [10-13].

Immuno-Inflammatory Responses

Severe SARS-COV-2 infection induce haemo-phagocytic syndrome due to the infiltration of pro-inflammatory monocytes, a rare

Table 1: Immune cell deviations in human COVID-19 lungs.

Features	Immune Events	References
Molecular	(i) Macrophage infection via antibody dependent receptor mediated endocytosis or pinocytosis (ii) Amplification of cytokine synthesis and secretion (iii) pyroptosis	(i) [14] (ii) [15] (iii) [14]
Surface markers	(i) DCs lack of surface markers (ii) appearance of an inhibitor surface markers DCs	[16]
Whole cell Immune Deviation	(i) appearance of intermediate phenotypes (ii) appearance of suppressor phenotypes (iii) DC-interferon axis (iv) impaired phase transition in alveolar epithelial cells (v) Bilateral alveolar macrophage positive feedback loop with T cells (vi) immune mediated pulmonary fibrosis	(i) [17] (ii) [17] (iii) [18] (iv) [19] (v) [20] (vi) [21][19]
Molecular inflammatory Events	(i) Infammosome formation (ii) Hyper-inflammatory responses (iii) Hypercytokinemia (iv) Pyroptosis	[22] [23] [15] [11] [14]
Gross Inflammatory Response outcomes	Plogs in all respiratory tracts, transudates and edema	[21]

condition expressed as an over excerbant inflammatory response due to development of hyper-cytokinemia together with depletion of the adaptive immune compartment which may explain the appearance of sepsis in many severe COVID-19 cases Gomez-Rail [23]. Macrophage activation syndrome MAS is a condition of systemic hyper-inflammation and often be noted in infection and malfunctioning. It is typified by marked up-regulated expression of pro-inflammatory cytokines. This sort of strong inflammation results in severe tissue injury. Macrophage within MAS state produce high amount of pro-inflammatory cytokine upon stimulation. Inflammation is known to destruct the balance between coagulation and fibrionolysis [14]. The inflammatory cytokines TNFalpha and IL1 instruct macrophage and monocytes to produce tissue factor TF. TF activate coagulation while IL1 anIL6 increase the production of plasmalogin activation inhibitor. Hence, overproduction of inflammatory cytokines along with MAS also promotes intravascular coagulation Otsuka and Senio [15]. Dys-regulated inflammatory syndrome DIS. DIS is generated by mononuclear phagocytes (a rich source of pro-inflammatory cytokines) upon encounter of the virus within the tissue continuum via two stage activation mechanisms which is not specific to the initiating virus. This is relevant to the case of SARS-COV-2 virus infection were age and predisposing comorbidities enhances the risk of severe outcome due to DIS [11].

Human severe SARS-COV-2 pulmonary infection leads to inflammation and tissue destruction with a consequence of an immune mediated fibrosis which remains even in to convalescent phase. In a group of severe pulmonary infected patients with COVID-19. IA aided CT scan were used to score fibrosis via fibrosis index IF. Twelve patients with severe COVID-19 were investigated for IF, they were sub-grouped into IFlo and IF hi. Mononuclear cell were collected from those patients and investigated by single cell RNA sequencing, IF hi group have shown low mononuclear phagocytic cell, low IFN gene profiling as compared to that of IFlo subgroup of patients. Mononuclear phagocyte could probe the prognosis of immune mediated ling fibrosis [16-21].

Monocyte Responses

In an in-vivo study setting SARS-COV-2 infection sensed by monocyte and macrophages, such sensation forms the inflammosomes that activate caspase I and gasdermin D leading to inflammatory cell death, the pyroptosis and release of potent inflammatory mediators. About 6% of blood monocyte of COVID-19 patients are infected with SARS-COV-2 virus. This virus infection of monocyte depends on the uptake of antibody-opsoinzed virus by FC gamma receptors. The internalized virus begins to replicate within the infected monocyte but infection is aborted and the infectious virus was not detected in the culture supernatant of the infected monocyte. Instead the infected monocyte undergoes pyroptosis mediated by activation of NLRP3 and AIM2 inflammosomes, caspase I and gasdermin D. In same culture settings, the addition of the COVID-19 vaccinee plasma does not promote AB dependent monocyte infection. Moreover tissue resident macrophages but not the infected epithelium and endothelium from lung autopsies from the deceased patients with COVID-19 have activated inflammosomes. The overall of findings suggest that ab-dependent SARS-COV-2 uptake by monocytes and macrophages triggers inflammatory cell death that abort the products of the infectious virus but cause systemic inflammation [14]. Though there was a report discounts the possibility of infection of both lymphocyte and monocytes [22,23].

Among the manifestation of SARS-COV-2 infection in man is the high systemic inflammation and immune dys-regulation. To obtains a mechanistic insight. An ex-vivo cell culture setting in which epithelial cells were co-cultured with monocytes and B cells. Epithelial cells were infected with SARS-COV-2 virus during the incubation period infected epithelial cells interacted with monocyte and B lymphocyte. Strong responses were induced both in monocyte and B cells with SARS-COV-2 inflammatory gene clusters which reproduce immune cell deviation. Similar to that deviation noted in the blood and lung myeloid cells from COVID-19 patients. Earliest infection of epithelial cells with SARS-COV-2 virus triggers inflammatory malformation of COVID-19 patients leading to raise of virus specific monocyte inflammatory phenotypes Leon et al. [24].

In a series of moderate COVID-19 patients, peripheral blood monocyte were investigated, the infection triggers inflammatory responses that stimulate an interferon stimulated gene driven phenotypes, cellular dysfunction epitomized by loss of HLADR receptor expression and induction of alarmin expression is documented in their features in severe cases. Pulmonary macrophages in COVID-19 were derived from infiltrating inflammatory monocytes are in a hyperactivated state resulting in determintal loop of pro-inflammatory cytokine release and recruitment of cytotoxic effector cells, thereby, exacerbating tissue damage in the site of infection [25].

Alveolar Macrophage Responses

In an experimental setting, two deceased severe COVID-19 patients were subjected within few hours to an anatomical and pathological study. Mucous plugs were found in all respiratory tracts, terminal bronchioles and pulmonary alveoli. Autopsy samples were processed and tissue samples were collected, sectioned and stained then examined. Real time PCR was performed to detect SARS-COV-2 Viral RNA. Flow cytometeric analysis was done to detect the direct binding of S protein and expression ofACE2 receptors on the macrophage surface. It was evident an extensive impairment of type I alveolar epithelial cells and atypical hyperplasia in type II alveolar epithelium with formation of halyn membrane, focal hemorrhage, exudation, pulmonary edema and consolidation. The mucous plug with fibrous exudates in alveoli together with alveolar macrophage dysfunction was the characteristic abnormalities. The SARS-COV-2 infection was detected in; alveolar epithelium, alveolar macrophages and hilum associated lymphoid tissue. SARS-COV-2 spike proteins interact with and bind ACE2 receptors. Infection of alveolar macrophages might derives cytokine storm [21].

SARS-COV-2 alveolitis were mapped in a human clinical setting in which broncho-alveolar lavage fluid samples were collected from within 48 of intubation from 86 severe COVID patients needing ventilation. In the majority of these patients the alveolar space is persistently enriched with alveolar macrophages and T cells

without neutrophils. Single cell RNA sequencing was done to five of the broncho-alveolar lavage fluids. Besides bulk and single cell transcriptomic profiling were suggesting that SARS-COV-2 infect alveolar macrophages, the infected alveolar macrophages in turn respond by recruiting T cells. These T cells release interferon gamma that triggers alveolar macrophages to secrete inflammatory cytokines and further promte T cell recruitments. Findings suggested that SARS-COV-2 causes slowly infecting, specifically-limited alveolitis in which aveolar macrophages incubating virus transcripts and T cells form positive feedback loop that derives progressive alveolar inflammation. Thus, SARS-COV-2 infected alveolar macrophages forms positive feedback loop with T cells in severe COVID-19 disease [20].

Tempts were made to investigate host responses at the level of lung tissue using single nucleus sequencing of 116000 nuclei from lungs of COVID-19 deceased in individuals and underwent rapid autopsies along with seven control individuals. Integrated analysis identified alterations in cellular compositions, transcriptional cell state and cell-cell interactions. The lungs from COVID patients were highly inflamed with dense infiltrates of aberrantly activated monocytes-derived macrophages and alveolar macrophages but had impaired T cell responses. Monocyte/macrophage derives interleukine 1B and epithelial cell derived IL6 were the unique features of COVID lung infection as compared to other viral pneumonias. Alveolar type II cells adopted an inflammation-associated transient progenitor cell state and failed to undergo full transition to into alveolar type I cells resulting in imparted lung regeneration with expansion of pathologic fibroblasts accounting for the rapidly ensuing pulmonary fibrosis in COVID-19 [19,26].

Dendritic Cells Responses

In a study on a series of convalescent COVID-19 patients peripheral blood mononuclear phagocyte cell were investigated in an in-vitro settings. Early infectious events of SARS-COV-2 with MPS has shown; impaired type I interferon responses, elevated inflammatory cytokine and chemokine levels. The virus even in absence of productive replication in the plasmocytoid DC mediate vigrous TLR7/TLR8 dependent production of both interferon type I and III and inflammatory cytokine as well as chemokine known to contribute to a state of hyper-cytokinemia' Cytokine Storm". Which were released from these DC in an ACE2 independent but Neuropilin-1 dependent mechanism. Viral sensing regulates pDC phenotype by inducing cell surface expression of PDL-1 marker, a feature of type I IFN producing cells. In comparison hospitalized COVID-19 patients displayed low frequency of circulating pDC with inflammatory phenotype. Early interaction of SARS-COV-2 and immune cells occurring invitro and proved ex-vivo indicate the role of pDC-interferon axis regulate antiviral state in asymptomatic and severe COVID-19 patients. Such findings may indicate crucial and protective role of pDC/IFN I axis in COVID-19 patients [18].

In an in-vivo experimental settings tackling moderate to severe COVID-19 patients. These patients were subjected to high dimensional flow cytometery focusing on MPS cells. It was evident that there were redistribution of monocyte subsets towards intermediate monocyte and general decrease in circulating DCs was observed in response to infection. Severe disease coincided with the appearance of monocyte-myeloid-derived cell suppressor-like cells and high frequency of pre-DC2. Such MPS cell phenotypic alteration and their precursors were cell lineage specific and associated with either the general response to infection of COVID-19 severity. This included an interferon-imprint DCs observed in all patients and a decreased expression of co-inhibitory molecules CD200R in pDcs, DC2 and DC3 subsets in the severely sick patients. Such findings stands as a prove for the MPS dys-regulation associated with severe COVID-19 patients [17].

DCs recognize viral infections and trigger innate as well as adaptive immune responses. COVID-19 severity is highly influenced by the host immune responses and modulation of DCs generation and functions. After the establishment of SARS-COV-2 infection, DCs could play an important role in the immunopathology of the disease. In a series of 65 COVID-19 patients covering mild, moderate to severe infection forms were subjected to analysis of DC circulating populations. Results of such analysis has shown long lasting reduction in DC subpopulation with an expression of functionally impaired – HLADR+ cells lacking DC markers. A higher CD163+ CD14+ cells among DCs subpopulations correlate with systemic inflammation. Depletion and functional impairment of DCs beyond the acute phase play a role in inflammatory responses of COVID-19 patients [16]

Circuit

In the molecular immune sense circuit means a communication form between two immune cells living with in one tissue continuum. In which one cell activated by an inducer, infection will produce mediator, cytokine that activate the other immune cell to produce other mediator, cytokine which in turn affect the first immune cell to produce other mediator. In severe COVID-19 pneumonia infection of alveolar macrophage lead them to produce T cell chemo-attractants. These T cells produce interferon gamma to induce inflammatory cytokine release from the alveolar macrophages and further promote T cell activation. Thus Alveolar macrophages containing the virus and T cells form a positive feedback loop that derives persistent alveolar inflammation [20,25]

Six Points Severity Index

Since studies performed on severe COVID-19 patients were from different nations and different geographical regions across the globe. As well as the sampling and techniques tempted were somewhat different. Thus to hypothetical suggestions for a COVID-19 severity index, one should hold four assumptions as; (i) The sense of severity is of relative homogeneity (ii) Different MPS cells have equal opportunity to face local or systemic viral loads (iii) The function of the MPS cell functions are of similar state and (iv) The invented index components are of equal weights in the evaluation consideration;

1. Low counts of DCs subpopulations in the peripheral blood stream, impaired function and loss of surface markers.
2. DCs-interferon axis function stand as an index of severity and viral persistence
3. Low count of broncho-alveolar macrophages and poor transition of type II to type I epithelial cells parallels with severity

4. Alveolar Macrophage-alveolar T cell are set on parallel with severity
5. Epithelial prior infection pave the way for alveolar macrophage and B cell infectious activation
6. Deceased COVID-19 patients associated with alveolar macrophage infection consequences, the pyroptosis and sepsis.

Conclusions

During clinical human SARS-COV-2 pulmonary infection forms, mononuclear phagocyte system cells and epithelial cells are prone to this virus infection. The infection of APS cells is of antibody dependent type. On APS cell infection virus replication cause molecular alterations in; cellular composition, cellular transcription state, and cell-cell interactions. Secretory protein exports in these infected cells are amplified leading to the production of pro-inflammatory and inflammatory cytokine. At the whole cellular levels infected APS cells undergoes immune deviations like; lack of cell surface markers, appearance of intermediate phenotypes, suppressor phenotypes, inhibitory marker bearing phenotypes as well as reduction in numbers in the peripheral blood stream. Reduction in numbers of APS cells as well as alveolar epithelial cell phase transition impairments were implicated with immune mediated pathological pulmonary fibrosis. Alveolar epithelial cell infection may triggers alveolar macrophage infection and B lymphocytes. Alveolar macrophage infection initiates bilateral positive feedback mechanisms with T lymphocytes. DC cells undergo long lasting reduction in numbers, functional impairments and lack of surface markers. DC functions together with interferons in an axis form leading to regulation of antiviral state in asymptomatic and severe cases. APS cell infections initiate haemo-macrophage syndrome, macrophage activation syndrome, and intravascular coagulation, implicated in immune mediated pulmonary fibrosis, pyroptosis, and terminated by sepsis.

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