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ARE THE PULMONARY MACROPHAGES ACTING AS KEY PLAYERS IN PNEUMONIA?

Medical Science

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ABSTRACT

Macrophages are the large eaters. These are the long lived phagocytes. Alveolar or pulmonary macrophages are unique cells because they roam about freely on the outer surface of lung, where they are exposed to a constant supply of inhaled phagocytized particles. These cells move over alveolar surface, scavenger dust particles, microorganisms and other debris. The attachment of antigens to macrophage is specific. All the macrophages have specific receptors for C3 component of complement as well as Fc component of antibody.

The C3 receptor promotes the adherence of antigen to macrophage by way of opsonisation antigen by the complement whereas the Fc receptors help in binding with in the antibody there by promotes the phagocytosis of antigen antibody complex. Macrophages are involved in the processing of antigens before they are presented to the T and B cells. When the antigen adherence with lymphocyte processing, receptors for the antigen, recognition takes place and thus the lymphocytes are induced to produce immunity. The macrophages that present antigens to T-helper cells (Th) should have MHC determinant of class 11 on the surface where as macrophage that present antigens to T-cytotoxic cells (Tc) cells should have the MHC determinant, it cannot cooperate and thus antigen presentation cannot occur, which is known as MHC restriction Macrophages are important secretory cells producing and secreting a number of substances such as components of complement system, hydrolytic enzymes, toxic forms of oxygen and the monokines.The monokines have regulatory effects on lymphocyte function. In some types of primary and secondary pneumonia, prominent features are destruction of lung tissue by the inflammatory process, a high incidence of abscess formation and the subsequent growth of pulmonary fibrosis and bronchiectasis.

KEYWORDS

Staph.pyogenes, Strep.pyogenes, Klebsiella pneumoniae, H.influenzae, Legionella pneumophila, Mycoplasma pneumonia ,Coxiella burnetii and Chlamydia psittaci

INTRODUCTION

Macrophages are innate immune cells present in every tissue and necessary for homeostasis.Macrophages sense and respond to pathogens and other environmental challenges and participate in tissue repair after injury (1) Macrophages have several origins during ontogeny and display great diversity(2)

Macrophages of different phenotypes recruited from the monocyte reservoirs of blood, spleen and bone marrow (3) Macrophage responses to pathogens that have been discussed extensively by others (4) Macrophages arise from succession of macrophage progenitors (5) CD115+ CD117+ monoblast-type cell, give rise to monocyte subsets (6).

Monocytes, make an appearance in lung tissue, will start to modify into larger cells (7) CD14 has been used as a marker in man (8) Mycoplasma pneumoniae can be collaborator with upper air way liaison (9) Late-onset VAP, caused by Gram-negative bacilli, S aureus, including methicillin-resistant, Pseudomonas aeruginosa (P aeruginosa), and Acinetobacter spp (10)

Chronological Record Of Significant Events

Pneumonia has been a common disease throughout human history (11) The word is from Greek (pneúmon) meaning "lung " (12)The symptoms were described by Hippocrates (c. 460–370 BC):

Streptococcus pneumoniae and Klebsiella pneumoniae, was performed by Carl Friedländer and Albert Fraenkel (13) In 1882 and 1884, respectively.

Christian Gram initial work introduced the Gram stain (14) Vaccination of infants against Haemophilus influenzae type B in 1988 (15)Pneumonia is an inflammatory condition of the lung affecting alveoli.(16) Pneumonia is caused by infection with viruses or bacteria .(17)

Defense Mechanisms

The mega eaters bind the bacteria, engulf and digest intracellularly wit hydrolytic enzymes.During emergency, more macrophages and neutrophils are initiated in digestion (18)

Lung Tissue

Ciliated columnar epithelium lines respiratory tract. Cilia trap dust and bacteria. The alveolar wall is lined by an epithelium consisting mainly of flattened squamous cells..

Research On Inflammasomes

Inflammasomes abide of a sensor protein and caspase-1. The caspase-1, which upon activation cleaves immature pro-IL-1ß and pro-IL-18 to the mature secreted forms (19)

Recent investigations have revealed an important protective role for the NLRP3 inflammasome during pneumococcal pnemonia (20)

Research on the Production of Interleukin-20

Cytokines limits bacterial clearance and lung inflammation during infection.(21)

This was originally called Lymphocyte activating factor(LAF). Originally observed to be secreted by macrophages and hence called monokines.but now it is known to be produced by nucleated cellsThe production of IL-1 is induced by the antigens,lectins and lymphokines from T-cells such as macrophage activating factor.It stimulate B-cell proliferation and synthesizes immunoglobulins.It activate T-cells and promote synthesis of lymphokines.It is endogenous pyrogen,hence induces fever. Sometimes even erythrocytes cross this barrier and result in hemoptysis (22,23)

Two independent macrophages prevail in the lung called alveolar macrophages (AMs) and interstitial macrophages (IMs), respectively. (24) While AMs exert their regulatory effects like the secretion of antimicrobials, nitric oxide (NO), tumour necrosis factor (TNF)-a and interferon (IFN)- and IMs to release interleukin (IL) 10 (25,26)

Macrophages, are classified basing on their activation as M1 and M2, analogous to the T helper cells Th1/Th2 paradigm.(27) M1 or an M2 phenotype has been associated with specific transcriptional control (28)Human and murine studies, dictate proinflammatory cytokine production in cells. (29)

Pulmonary macrophages: key players in defense of the airways Microphages are the immune cells of lung. Helps in innate defense (30)

Cough is an explosive expiratory manoeuvre that is reflexively or deliberately intended to clear the airways. (31) The main cause of death in children, all over the globe is pneumonia (32) The macrophages exhibit phagocytosis. The infectious microbes were digested intracellularly. Thus the microbes enter into the nasal passage, glottis and alveoli were killed.(33) The cell to cell signals, initiate inflammatory responses and recruit activated neutrophils into the alveolar spaces. (34)

Efficient clearance of apoptotic neutrophils by alveolar macrophages also requires the coordinated expression of soluble factors such as ß 2-glycoprotein. (35)Cellular mechanisms involved in natural resistance The cellular defenses are among the adaptive of all mechanisms available to resist the aggression of the body by parasitic microorganisms. Inflammation was regarded as useful homeostatic mechanism, primarily involving vascular mechanism.

The cellular pattern of the response varies a good deal and depending on the type of tissue affected and the kind of infective organism. The variations may be thought of in terms of variations in the cell parasite relationship. For instance, it would seem that the two bacteria Staphylococcus pyogenes and Mycobacterium tuberculosis both at first stimulate the exudation of macrophages(Polymorphonuclear leukocytes).But eventually they produce quite different inflammatory lesions. We can argue plausibly that S aureus is able to multiply rapidly outside cells and to produce an exotoxin.

This will continue the irritation of neighbouring blood vessels so that the polymorph emigration continues. Eventually the result is, a typical pus containing abscess. The story with Mycobacterium tuberculosis is different The diapedesis of polymorphs comes to an end and an impressive accumulation of macrophages occurs, partly derived from blood stream and partly from local multiplication of resulting cells which were there in the tissue from the first.

Mycobacterium tuberculosis lacks a potent exotoxin, but having been taken up by phagocytes is able to grow slowly inexorably within the cytoplasm of these cells. The microphages first take up the such bacilli but are either rather steadily killed by the latter or, in any case disintegrate, and are themselves ingested by by the newly arrived macrophages, which continue to act as host to the bacilli. (36)

Macrophages in inflammation and its resolution Labrousse et al.(2011) described the lysosomal movements and fusion.Janko et al. (2011) (37) Korns et al. (2011) outline apoptotic cell clearance by macrophages. (38) The environmental factor, hypoxia, effects on monocyte/macrophage activation. (Rahat et al. 2011). (39)

Infections of the lung *Pneumococcal pneumonia* (Acute lobar pneumonia) The pneumococci are primarily concerned with infections of the upper and lower respiratory tracts, but are carried in the throat by many healthy persons. They are the commonest primary pathogens in lobar, lobular and bronchial-pneumonia, and bronchiolitis and are frequently associated as secondary pathogens. The pneumococci are therefore, major contributors to morbidity and economic loss since respiratory infections are responsible for 30-40% of illness requiring medical attention. They are particularly frequent and severe at extremes of life.

Staphylococcal pneumoniae Due to *Staphylococcus aureus* may occur either as a primary respiratory infection or as a blood borne infection from a staphylococcal lesion elsewhere in the body, for example osteomyelitis. The second condition essentially one of pyemic abscess formation in the lungs. Unless an empyema is produced by rupture of an abscess in to the pleura, the pulmonary lesion may pass unnoticed overshadowed by the severe general illness.

Primary Staphylococcus pneumonia although it occurs much less frequently than pneumococcal pneumonia, is a relatively common illness especially as a complication of influenza. . *Klebsiella pneumoniae,* Pneumonia due *to Kl. pneumonia* is a rare disease with a high mortality. There is usually massive consolidation and excavation of lobes, the upper lobe is being most often involved, with a profound systemic disturbance and chocolate colored sputum. It is usually sensitive to chloramphenicol, mezlocillin and cefotaxime.

Legionella pneumonia, bacillus may be transmitted in water droplets for showers, particularly from warm climates. It is often serious and sometimes fatal. it is characterized by gastrointestinal symptoms, mental confusion, hyponatremia and proteinuria. The organ is sensitive to erythromycin and rifampin. Bordetella pertussis It causes bacterial respiratory infections of childhood in communities not effectively protected by vaccination.

The name whooping cough is given to this infection because of the tendency for a paroxysm of coughing to end with a long inspiratory high-pitched note or whoop This disease in its typical form is prolonged and debilitating and may affect 70-8-% of unprotected children with a high incidence and severity of attack in infants under two years of age. *Pseudomonas aeruginosa* It is a Gram-negative bacillus, non-sporing and non-capsulated and usually motile. The lungs of children with cystic fibrosis are very susceptible to infection with *P. aeruginosa.* prolonged carriage is often associated with the emergence of the mucoid forms of .P.aeruginosa and further pulmonary deterioration.

Chlamydia pneumoniae Briefly, a pleomorphic bacterium which is susceptible to tetracyclines through a few strains are sensitive only to erythromycin. Most cases occur in children and young adults. Maculopapular rashes and hemolytic anemia meningoencephalitis occur rarely. Coxiella burnetii It is responsible for Q-fever. Endocarditis may occur, as well as pneumonia. Secondary pneumonias This group sometimes referred as non specific or aspiration pneumonias. Acute bronchopneumonia This type of aspiration pneumonia is invariably preceded by branchial infection, which accounts for the widespread patchy distribution of the lesions.

Benign aspiration pneumonia This type of secondary pneumonia is due to the aspiration of infected secretion into the lungs during the course of an upper respiratory infection such as coryza or sinusitis.It is thus often associated with segmental pulmonary collapse.The organism causing pneumonia, being derived from upper respiratory tract are generally of low virulence and degree of systemic disturbance E.g usually slight. (40)

Reactive oxygen species (ROS) is not required for killing of S. pneumoniae by alveolar macrophages (41) Neutrophil granule serine proteases, such as cathepsin G and neutrophil elastase, are required for the effective killing of ingested S. pneumoniae .(42) Three enzymes are involved primarily in the production of hydrogen peroxide during pneumococcal metabolism.(43) *Streptococcus pneumoniae* colonizes the nasopharynx as do other pathogens such as *Moraxella catarrhalis, Haemophilus influenzae, and Neisseria meningitides.* (44)

Factors In The Invasiveness Of Microorganisms

Certain microorganisms may be invasive and virulent because they survive with in phagocytic cells and are resistant to enzymatic attack. Although various factors contribute to the observed invasiveness of microorganisms, it must be concluded that this behavior is an expression of inherent biochemical properties not yet understood. Invasiveness as such is by no means synonymous with disease production Biochemical tissue constituents . Certain animal tissues are resistant to specific bacteria (Eg. Bacillus anthracis) because of their content of basic polypeptides, which have antibacterial properties.

Biochemical constituents may determine tissue resistance to infection. Beta lysin of serum can kill gram positive bacteria. Many normal tissues have a high inherent ability to inhibit proliferation of microorganisms. The resistant is severely impaired by trauma, foreign bodies ,disturbances ,and depressed inflammatory response (X-ray radiation, corticosteroids, anti-cancer drugs,)

Research On Inflammatory Response

This begins with local arterioles and capillaries, from which plasma escapes. Edema fluid accumulates in the area of injury, and fibrin forms a network and occludes the lymphatic channels, tending to limit the spread of organisms. Polymorph nuclear leukocytes in the capillaries stick to the walls. This migration is stimulated by substances from the inflammatory exudate (chemotaxis) The phagocytes engulf the microorganisms and intracellular digestion begins.

Soon the PH of the inflamed area becomes more acid, and the cellular proteases tend to induce lyses of the leukocytes. Large mononuclear macrophages arrive on the site and, in turn, engulf leukocyte debris as well as microorganisms and pave the way for resolution of the local inflammatory process. Among probable mediators are lymphokines and derivatives of arachidonic acid, including prostaglandins leukotrienes and thromboxanes.

Drugs that inhibit the synthesis of prostaglandins (by blocking the enzyme cyclooxygenase) acts as inflammatory agents. Different stages in inflammatory sequence may predominate with different microorganisms as the inciting cause of the inflammation.The early edema fluid may actually promote bacterial growth.

Staphylococcus tends to limit their spread through extensive lymphatic thrombi, fibrin walls etc. Precipitated by coagulase, where as hemolytic streptococci, through the activity of streptokinase(fibrinolysin) and hyaluronidase, tend to spread rapidly through the tissue. Phagocytosis and intracellular residence are destructive to some bacteria(some pyogenic cocci),where as the others (Eg. tubercle bacilli) they serve as means of transport and protection and even of multiplication. Investigation of Pneumonia An attempt should always be made to establish a positive microbiological diagnosis, though this is not always possible, before specimens are submitted for examination. Direct smear examination of sputum by Gram and Ziehl -Neelsen stains may given an immediate indication of possible pathogens,and indicate what treatment should be prescribed.

Culture and sensitivity testing should be carried out. Blood culture should be performed in patients with severe pneumonia, and may yield a positive result ,when sputum examination is negative, particularly in pneumococcal pneumonia. Pneumococcal antigen may be detected in serum. A total and differential white blood count is often low in patients with viral infection and a high neutrophil polymorph leukocytosis favors bacterial infection. The ESR is usually elevated, but is of no help in diagnosis. Arterial blood gas studies are of vital importance in those with a previous history of chronic respiratory disease.

Radiological examination is essential for confirmation of the diagnosis. Trans bronchial lung biopsy or microscopical examination of bronchial pneumonia brushings or washings confirming a diagnosis of *Pneumocystis carinii* (45)

Bronchial and pulmonary secretions or exudates are often studied by examining sputum.The most misleading aspect of sputum examination is almost inevitable contamination with saliva and mouth flora.The presence of many squamous epithelial cells suggest heavy contamination with saliva; more number of PMNs suggests a purulent exudate. Sputum may be induced by the inhalation of heated hypertonic saline aerosol for several minutes. (46)

Legionella-Urine legionella antigen test,Sputum staining with direct fluorescent antibody test (DFA),Culture Chlamydia pneumoniae-Serological testing,Culture,PCR Mycoplasma Usually clinical.Serum cold agglutinins and serum mycoplasma antigen test,Culture Streptococcus pneumoniae-Urine pneumococcal antigen test, Culture.

CONCLUSION

Most of the cells of the immune system derived from hematopoietic system. Phagocytic cells are found in the circulation (Monocytes and granulocytes) and reside in the tissues (macrophages).Each cell type expresses characteristic surface molecules (CD3,CD4,CD8..) Alveolar or pulmonary macrophages present freely on the outer surface of lung.

These cells scavenging the dust particles microorganisms and other debris.The primary function of macrophage is phagocytosis. The macrophages by their property of amoeboid movement, put forth pseudopodia which help in engulfing any solid particle such as the invading microorganisms.

The macrophages have lysosomal granules, containing acid hydrolases and degradative enzymes with which it destroys the phagocytosed substances. The attachment of antigens to macrophage is specific. All the macrophages have surphase receptors for C3 component of complement as well as for Fc component of antibody.

The macrophages are involved in processing of antigens before they are presented to the T and B cells.(47)

Macrophages contribute to phagocytose of many bacteria like Staphylococcal pneumoniae, Klebsiella pneumoniae, Bordetella pertussis, Pseudomonas aeruginosa, Chlamydia pneumoniae, Mycoplasma pneumonia, Coxiella burnetii that cause pneumonia.

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