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Review on immunity in viral infections

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Abstract: Novel interactions and effective modelling of the immune function is necessary for the development of antiviral mechanisms against the infectious viral disease . The immune system is intrinsic to health and is variable in humans due to the heritable and non-heritable influences. The key to identifying the risk of immune mediated and infectious diseases must be to understand and know the human immune system. The main components that develop immune responses include natural killer cells, cytokines, vaccines, Helper T cells. The cytokine and the chemokines play a crucial role in the induction of the antiviral mechanisms thereby deteriorating the level of viral replication. The natural killer cells are effector cells of the innate immune systems. The helper T cells play a pivotal role in inducing cell mediated immunity. The plasmid DNA vaccines induce strong and long lasting humoral (antibodies) and cell mediated (T- helper cell , other cytokine function cells and cytotoxic T cells), immune response without creating a risk of infection to the host's immune system. The cell mediated immunity is a type of immune response that involves the activation of the phagocytes, cytotoxic T-lymphocytes and various cytokines in response to the antigen without the production of antibodies. The mucosal immune system is an adaptive immune system associated with mucosal sites such as the gut mucosa that comprises Peyer's patches, cryptopatches, isolated lymphoid follicles in the gut antimesenteric wall, and the mesenteric lymph nodes. The aim of the review is to highlight the various antiviral defense mechanisms to boost the immunity.

Keywords: cytokines; Natural killer cells; cell mediated immune response; Helper T cells innovative technique

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INTRODUCTION

Viral infections being about a profound challenge for the host survival ,wherein the capacity of the virus to replicate and /or persist in the host is used for the antiviral defense mechanisms (Davis, Tato and Furman, 2017). The human immune system is highly variable between the individuals, but it is considerably stable over time within a person. It helps in the protection against infectious agents through the resistance of the B and T cells (Germain and Schwartzberg, 2011). T cell lymphocytes protect the body and provoke the cell mediated immunity. They activate cytotoxic T cells and stimulate antibody production. It is necessary to understand the mechanisms of an individual's immune system as they will help to develop target mechanism which thereby modulates the immune responses,either for an immune mediated disorder like chronic inflammatory disease/allergy or to create a desired immune response against vaccines,pathogens or tumours (Hayday and Peakman, 2008; Gibbons *et al.*, 2014). Antiviral defense mechanisms are variable and range from primitive,constitutively expressed,non-specific defense mechanisms to sophisticated mechanisms that are particularly induced to viral antigens (Qi *et al.*, 2014). COVID19 is caused by SARS-COV2 and is a causative agent which mainly targets the human respiratory system.The virus incubation period varies from 0-24 days. The herd immunity will begin to take effect when a population reaches the herd immunity threshold value, namely when the proportion of individuals who are immune to the pathogen crosses $1 - 1/R_0$. The sustained transmission cannot occur at this point , thereby declining the outbreak. The two possible approaches to build widespread SARS-CoV-2 immunity are a mass vaccination campaign, which requires the development of an effective and safe vaccine, or natural immunization of global populations with the virus over time. The potential therapeutic treatments for COVID 19 include disease-modifying anti-rheumatic drugs (DMARDS), such as hydroxychloroquine and tocilizumab which has been confirmed to trigger immune hyperactivation (Zhao *et al.*, no date).

Latency is the ability of a pathogenic virus to stay dormant within a cell and is denoted as the lysogenic part of the viral life cycle (Roederer *et al.*, 2015) . Latent viral infection is a type of infection wherein after the initial infection, proliferation of the virus ceases, however , there is no eradication of the viral genome (Shen-Orr *et al.*, 2016) . Acute viral infection is a form of viral infection that is characterised by rapid onset of disease, wherein there is a relative period of brief symptoms, and the resolution exists within days. They are accompanied by the

production of infectious virions and cause the deterioration of the host's immune system (Gregersen and Olsson, 2009). These infections contribute to an equilibrium process whereas chronic viral infection is a process in which there is presence of dynamic and metastable equilibrium (Bach, 2002),(Andres-Terre *et al.*, 2015).

The cell mediated immunity is a type of immune response that doesn't require antibodies. It involved the activation of the phagocytes, cytotoxic T-lymphocytes and various cytokines in response to the antigen. The mucosal immune system is an adaptive immune system that is present in the gut of the mucosa, intestinal intraepithelial, lymphoid follicles and provides protection against pathogenic bacteria by occupying the ecological niches for bacteria in the gut. They play a vital role in nutritional supply for the host by synthesizing vitamin K and some of the components of the vitamin B complex.

Recent studies for attaining immunity have shown that the vancomycin resistant enterococcus [VRE] ia attaining virulence as Methicillin-resistant *Staphylococcus aureus* (MRSA) (Ashwin and Muralidharan, 2015). Several investigations has proven that the Carbapenems are the drug of choice for various nosocomial infections caused by multidrug-resistant *Acinetobacter baumannii* strains (Girija *et al.*, 2019),(Priyadharsini *et al.*, 2018b). However periodic surveillance is necessary with the association of the emergence of *A. baumannii* strains in the form of MDR-Ab, XDR-Ab (Girija As and Priyadharsini J, 2019). Hene it's evident from the study that the *A. baumannii* traits have different kinds of immune responses including antimicrobial resistance patterns and associated genes (Girija, Jayaseelan and Arumugam, 2018),(Priyadharsini *et al.*, 2018a).The blaTEM, blaSHV and blaCTX-M plays a vital role in providing antibiotic sensitivity and resistance of ESBL from the *A.baumannii* strains (Smiline, Vijayashree and Paramasivam, 2018).

In addition to it,most of the herbal mouthwashes with chlorhexidine have vital immune actions that can kill species of *Candida* and *Staphylococcus* (Selvakumar and Np, 2017). In certain studies the efficacy of the mouth rinse to maintain the oral health of the patients were noted (Shahana and Muralidharan, 2016). Inorder to prevent compromising on oral hygiene ,the chlorhexidine and the hydrogen peroxide effects was assessed to detect the reduction of the levels of the spirochetes thereby increasing the immunity of the host . The rate of the bactericidal activity was evaluated by noting the inhibitory effects of the medicaments on *Enterococcus faecalis* i*n vitr*o (Marickar, Geetha and Neelakantan, 2014). Moreover the antibacterial activity of the orange peel oil on *Streptococcus mutans, Enterococcus* was investigated inorder to decrease the incidence of dental caries (Vaishali and Geetha, 2018). The anti inflammatory of the bay leaf was determined along with its medicinal properties which is commonly used as an analgesics and non steroid anti inflammatory drugs (M, Geetha and Thangavelu, 2019).

Our department is passionate about research we have published numerous high quality articles in this domain over the past years (Abraham *et al.*, 2005; Devaki, Sathivel and BalajiRaghavendran, 2009; Neelakantan *et al.*, 2010, 2015; Arja *et al.*, 2013; Ramshankar *et al.*, 2014; Sumathi *et al.*, 2014; Surapaneni and Jainu, 2014; Surapaneni, Priya and Mallika, 2014; Ramamoorthi, Nivedhitha and Divyanand, 2015; Manivannan *et al.*, 2017; Ezhilarasan, 2018; Ezhilarasan, Sokal and Najimi, 2018; J *et al.*, 2018; Ravindiran and Praveenkumar, 2018; Malli Sureshbabu *et al.*, 2019; Mehta *et al.*, 2019; Krishnaswamy *et al.*, 2020; Samuel, Acharya and Rao, 2020; Sathish and Karthick, 2020)

The aim of this review is to analyze the importance of facilitating natural killers, cytokines, lymphocytes , B and T cells , and vaccines for antiviral defense mechanisms.

LOCAL IMMUNITY

The local immunity can be initiated by antigens presented to immunocompetent cells both within or outside the respiratory tract. These infections are localised and don't penetrate to other regions of the body. The main determinants for the degree of local secretory gA synthesis are the site of antigen processing and/or presentation, and the nature of the antigen itself. GALT (Gut Associated Lymphoid Tissue) is an important contributor to the development of local antibody response in the respiratory tract. After the oral immunization in case of patients with live poliovirus, specific IgA can be detected in nasopharyngeal secretions (Ogra *et al.*, 1968). The role of the local immunity includes the development of virus specific antibody and cell-mediated immune response in the respiratory tract in protection against and in pathogenesis of diseases has been studied with a large number of viruses. These include poliovirus, other enteroviruses, influenza, parainfluenza, rubella, measles, adenovirus, and RSV [respiratory syncytial virus] (Hall, 1984) . However, infections with RSV and, less frequently, with other respiratory viruses have been clearly observed to develop bronchial hyperreactivity and exacerbation of asthmatic episodes in childhood (McIntosh *et al.*, 1973). Studies carried out with RSV, thereby proves that it will serve as an informational model whose implications should be applicable to other respiratory pathogens. Moreover , the phagocytosis of RSV-antibody immune complexes stimulates granulocytes to release inflammatory mediators and mediators of airway obstruction . Patients undergoing infection-induced bronchospasm often exhibit other broad based clinical and immunologic abnormalities affecting other dietary and inhaled antigens. The possible mechanisms responsible for these changes include increased permeability of the respiratory epithelial barrier to

other environmental agents during viral infections. Thus it can be comprehended that RSV and other viral infections may function as adjuvants for other antigens inhaled during acute infection.

HERD IMMUNITY

The ongoing SARS-CoV-2 pandemic has caused over 73,43,977 clinically confirmed cases of COVID-19 and has claimed more than 4,14,129 lives worldwide (as of June ,2020). Numerous clinical trials are done to evaluate novel vaccine candidates and drug repurposing strategies for the prevention and treatment of SARS-CoV-2 infection across the world (Huang *et al.*, 2020). However, it is still unknown whether these trials will produce effective interventions for the treatment of COVID-19.

With the absence of a vaccine, building up SARS-CoV-2 herd immunity through natural infection is theoretically possible. However, there is no appropriate straightforward/ ethical path to reach this goal, as the societal consequences of achieving it are devastating drastically. In the communities where there is uniform spread of the virus, the outbreak gets gradually dropped.

From the onset of SARS-CoV-2 spread, various studies have estimated the basic reproductive number value (R_0) of the virus to be in the range of 2 to 6. Assuming a rough R_0 estimate of 3 for SARS-CoV-2, wherein the herd immunity threshold is approximately 67%. This means that for the infection to decline after it's begun , the proportion of individuals with acquired immunity to SARS-CoV-2 in the population must exceed 0.67. The R_0 values relies on several keys, including homogeneous mixing of individuals within a population and that all individuals develop sterilizing immunity—immunity that confers lifelong protection against reinfection—upon vaccination or natural infection (Delamater *et al.*, 2019). Inorder to establish the herd immunity, the immunity generated by vaccination or natural infection must prevent onward transmission, not just clinical disease. Once the herd immunity threshold level is reached, the efficacy of the herd immunity mainly depends on the strength and duration of the immunity acquired (Anderson and May, 1985). For pathogens in which lifelong immunity is induced, as in the case of measles vaccination or any other forms of infection, herd immunity is highly effective and can prevent pathogen spread within a population.

MUCOSAL IMMUNITY

Mucosal Immune System, commonly called MALT is used to stimulate adaptive immune response in a particular set of body tissues. The mucosal surfaces of the various parts of the body are particularly vulnerable to infection. These are thin and permeable barriers to the interior part of the surfaces of the body because of their physiological activities in gas exchange (the lungs), food absorption (the gut), sensory activities (eyes, nose, mouth, and throat), and reproduction (uterus and vagina). The need for the permeability of the surface lining of these sites creates obvious vulnerability to infection and causes these infectious agents to invade into the human body through these routes. The gut primarily acts as a portal of entry for a wide range of foreign antigens in the form of food. The immune system has evolved various mechanisms to avoid a vigorous immune response to food antigens on one hand and on the other, to detect and kill these pathogenic organisms that enter through the gut (Fine, 1993). Along with the induction of the immune responses from these responses there is also presence of lymphocytes and plasma cells in the gut wall which represent as effector cells of the gut immune system. The most dominant antibody isotype of the mucosal immune system is IgA. These polymeric immunoglobulin receptors bind polymeric IgA or IgM and transport the antibody by transcytosis to the luminal surface of the gut. Upon reaching the luminal surface of the enterocyte, the antibody is released into the secretions through the proteolytic cleavage of the extracellular domain of the polymeric IgA receptor. The secreted IgA will bind to the mucus layer overlying the gut epithelium where they can bind to and neutralize the gut pathogens and their toxic products (Anderson and May, 1985) .

CELL MEDIATED IMMUNITY

The Cell mediated immunity is found to be of major importance in the resistance to a variety of facultative and obligate intracellular organisms. CMI plays a pivotal role in elucidating various biological processes such as rejection of the allografts,resistance to tumor and graft versus host reactions. These immune responses are initiated when the T lymphocytes are specifically sensitised by contact with foreign antigens. The contact between the lymphocytes and antigens occur either at the site of the infection or in the lymph nodes in the peripheral areas through which the organisms have invaded. The T lymphocytes in the lymph nodes localise and sensitize in periarteriolar areas which are mainly thymus dependent areas (Henney and Waldman, 1970).

The intracellular pathogens are microorganisms that reside inside cells at some stage of infection. They can be obligate or facultative depending on whether the growth inside cells is required for replication and survival of the microorganism. The intracellular cells produce inflammatory responses that cause cell damage and affect the tissue level penetration. These pathogens are not immediately accessible to serum antimicrobial molecules such as antibody and complement. They are mainly located in the extracellular space before they enter cells and that antibodies are multifunctional molecules that can mediate a variety of effects, including opsonization and toxin neutralization. Antibodies will also bind to antigens of intracellular pathogens on the surface of the host and will

develop antibody-dependent cellular cytotoxicity and/or complement-mediated lysis. In case of immunoglobulin A (IgA) antibodies that neutralize viruses inside cells have been described, and DNA-binding autoantibodies have been shown to cross the cellular and nuclear membranes and to bind to cellular chromatin (Henney and Waldman, 1970; Beiting and Roos, 2011).

CYTOKINES AND CHEMOKINES

Cytokines and chemokines are produced mainly by macrophages and T-lymphocytes which play a pivotal role in producing antiviral immune responses. They result in the induction and orchestration of various antiviral mechanisms including alteration of the expression of the MHC molecules, adhesion molecules , co-stimulatory molecules and cause direct activation / deactivation of immune cells (Vilcek, 1996).

Cytokines play a crucial role in the regulation of Nitric Oxide (NO) production. The NO has various antimicrobial activity against a wide range of intra and extracellular microbes including virus (Taub *et al.*, 1993)· They induce iNOS , an enzyme which catalyzes NO production in large quantities. According to few studies, it was noted that the tissue culture cells infected with VV iNOS produce high levels of NO, resulting in considerable reduction in levels of viral replication (Rolph *et al.*, 1996).

Most type I cytokines decrease the pathogenicity of the viral infections including IL-2, IL-12, interferon gamma and TNF-2.However in contract , the type2 cytokine produced a drastic increase in virus virulence to rVV-encoded IL-4.

VACCINE DEVELOPMENT

Vaccination is a major global health priority . DNA is an antigen encoding plasmid which open introduction into the body is capable of directing in vivo expression of that particular protein (Pasetti *et al.*, 2011). They offer a unique method of immunization that can overcome most of the deficits of traditional antigen based vaccines. The plasmid DNA vaccines tend to induce strong and long lasting humoral (antibodies) and cell mediated (T- helper cell , other cytokine function cells and cytotoxic T cells), immune response without creating a risk of infection to the host's immune system. The various advantages of these antigen-containing vaccines include they are economical, relative ease of usage easily manufactured with heat stability, rapid development of immune responses against the new strains of pathogens (Gaucher *et al.*, 2008).

The specific immune responses are developed due to the combination of the following factors: efficient antigen presentation by virtue of in vivo synthesis, prolonged antigen synthesis and the adjuvant effect of CpG immunostimulatory motifs (Reed, Orr and Fox, 2013). The DNA virus has been used to show local and distal mucosal and systemic responses through the administration by mucosal route along with treating chronic viral infections. Recent studies have proven that sufficient awareness needs to be given to the patients and the dental practitioner about the significance of the Hepatitis B vaccine (Pratha, Ashwatha Pratha and Geetha, 2017).

T-CELLS

Humoral immunity involves the production of B and T cells . The T- independent antibody isotopes (Ig M,IgG3). However, for including longer-lasting T-dependent antibody responses (like IG1,IgG2a), the B cell must be stimulated by cytokines secreted from the activated T helper cells (Denney *et al.*, 2010). T cells are a type of cells that produce cell -mediated immunity. They play a major role in recognizing antigen presented on cell surfaces through molecules encoded by major histocompatibility complexes (MHC) of genes (Vleminck and De Vleminck, 2013). Few T cells, normally CD8+ are activated by MHC class I antigens present on cells which will thereby differentiate into cytotoxic T lymphocytes (CTL). CTL acts both as cytolytic and non-cytolytic mechanisms on infected cells will destroy them and bring about apoptosis and reduce the ability of the pathogen to replicate in that cell. Recent studies have reported that the N6-methyladenosine (m6A) methylation which is one of the modifications of RNA plays a vital role in the regulation of the blood pressure in hypertensive patients (Paramasivam, Vijayashree Priyadharsini and Raghunandhakumar, 2020).

NATURAL KILLER CELLS

Natural Killer plays a critical role in contributing to viral control and viral clearance associated during the initial acute phase of viral infection and chronic infection which contributes to virus- assisted pathology. NK cells mediate the anti-viral functional (Dong *et al.*, 2000; Foley *et al.*, 2012). They are helpful in preventing viral infections such as cyclomegalovirus , influenza virus Hiv-1 and Hepatitis C virus (Achdout *et al.*, 2010). The natural killer cells mediated cytolysis by a number of mechanisms. such as exocytosis of cytoplasmic granules containing perforin and granzyme , Fas ligand - mediated induction of apoptosis , antibody - dependent cellular cytotoxicity , ADCC (Virgin and Walker, 2010),(Katz *et al.*, 2004). They play an active role as immune regulatory cells ,bridging ; innate and adaptive immune response as they produce cytokines and chemokines (Owen *et al.*, 2007). Parasites have developed a wide range of mechanisms that they use to evade or manipulate the host's immune response and establish infection. In case of a chronic infection with pathogens including malarial parasites, soil-transmitted helminths, *Mycobacterium tuberculosis* and viruses such as HIV may affect a third of

the human population of some developing countries. There is various evidence that shows that co-infection with these pathogens may alter susceptibility to other important pathogens, and/or influence vaccine efficacy through their effects on host immune responsiveness. Most of the host-parasite interactions influence the progression and control of infection to individual pathogenic microorganisms . Hence it can be comprehended that the infectious disease susceptibility and pathogenesis are influenced by concurrent parasite infections which will help the design of more effective treatments to control the spread of infectious diseases. In case of some helminth-derived ES products possessing potent immunoregulatory properties, these could be sufficient to suppress allograft rejection (Johnston *et al.*, 2015). Recent advances for the candida treatment process involve the bioactive components *A. nilotica* which possess the inhibitory potential against these antigens (Shahzan *et al.*, 2019).

CONCLUSION

Recent technological advances have enabled the immunological system to reveal the composition of immune cells and proteins of particular individuals. The Human Immune system is highly variable and is the key for defining the risk of various immune mediated and infectious diseases. Antiviral defense mechanisms are particularly induced to viral antigens with the help of natural killers, cytokines lymphocytes, B and T helper cells,vaccines for sustaining the human lives and provide resistance towards viral infection. Cytokines and chemokines induce the anti-viral mechanisms in infected cells, regulate negatively IL-12 and activate Natural Killer cells. They also play a crucial role in the regulation of Nitric Oxide production thereby reducing the levels of viral replication . DNA vaccines offer a unique technique for immunization in which the antigen synthesized in vivo offer direct introduction of its encoding sequences. They appear to induce strong and long lasting humoral antibodies and cell mediated T helper cells , other cytokine function cells and cytotoxic effects by virtue of their sustained *in vivo* antigen synthesis. The T cells are a type of cells that produce cell-mediated immunity and play a major role in recognizing antigens present on the respective cell surface . The Natural killer cells are effector cells of the innate immune system and are considered to be a vital component against the control of viral infection. They are generally large lymphocytes that lack T cell receptors and modulate adaptive immune responses. Therefore this review focuses on the need for an immediate and appropriate immune response against virus for developing a protective immunity against infectious viral disease. The augmenting factors that improve their function are very essential for sustained defense mechanisms.

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