Effects Of Host Age On The Immune System

Introduction

Longevity is determined by an effective cross-talk between deleterious processes that act on an organism over its lifetime and the physiological responses that promote effective homeostasis (Ponnappan and Ponnappan, 2011). Age?related changes of the immune system play a role in the increased susceptibility of elderly individuals to infectious diseases, vaccination failures, including the potential onset and/or progression of autoimmunity and neoplasia (Weiskopf et al., 2009). Immune senescence affects various cell types in the bone marrow and the thymus, mature lymphocytes in the peripheral blood and secondary lymphatic organs, as well as elements of the innate immune system. Despite the fact that the aging process affects both branches of the immune system, the innate immune response seems to be better preserved, while more severe, often detrimental, age?dependent changes occur within the adaptive immunity (Franceschi et al., 2000).

Immune System

The immune system is the basic defence mechanism present in all animals to protect against infections caused by pathogenic organisms. It involves a complex network of specialised cells (Noakes and Michaelis, 2013) and their products, each with its own specific function, performing in synergy. There are two fundamentally different types of responses; the innate (natural) immune system which acts as the hosts' first line of defence and the adaptive (acquired) response with the ability to maintain specificity in their defence (Quesniaux et al., 2005) through antigen specificity, allowing for more robust defence mechanisms to be activated more rapidly upon reoccurrence of the specific pathogen (Weng, 2006), thus the term 'acquired immunity'. Some articles report about an additional defence layer before encountering the innate and adaptive cells of the immune response. This layer is made up of enzymes and mucus which form surface barriers acting to directly kill harmful microbes or inhibit the attachment of the microbe (Delves and Roitt, 2000), to prevent entry into the host. This defence mechanism is broadly grouped to be a part of the innate immune response.

Although described as contrasting separate arms of the host response, the innate and adaptive systems act together with components of the innate system contributing to the activation of the adaptive response, and cells of the adaptive system amplifying their responses by recruiting innate effector mechanisms to control invading pathogens. Thus, communication between these systems is essential for a robust immune response (Noakes and Michaelis, 2013).

Immune Development

Cells of the immune system develop and mature during foetal life (Simon et al., 2016). These cells derive from haematopoietic stem cells (HSCs) within the bone marrow (Noakes and Michaelis, 2013), and go on to differentiate into cells of the innate immune system – phagocytic cells (neutrophils, monocytes and macrophages), cells that release inflammatory mediators (eosinophils, basophils, and mast cells) and natural killer (NK) cells, and cells of the adaptive

response – B and T lymphocytes (Delves and Roitt, 2000).

Regarding lymphocytes, the pluripotent HSC first develops into a common lymphoid progenitor cell which later develops into progenitor T or B cells. Progenitor T cells migrate from the bone marrow to the thymus to undergo maturation while B cells mature within the bone marrow (Quesniaux et al., 2005). Once mature, B and T lymphocytes travel to secondary lymphoid organs such as the lymph nodes, tonsils, spleen, Peyer's patches and mucosa associated lymphoid tissue (MALT) where they reside until activated through a process known as antigen presentation to become activated. Both B and T lymphocytes are able to differentiate into memory cells which are responsible for the ability of the adaptive immune system to maintain specificity in their defence.

Although development of the immune system begins in-utero, it is still relatively immature at time of birth and will continue to develop throughout life as the individual is exposed to a myriad of micro-organisms capable of causing disease (Simon et al, 2015). The immaturity of the immune system at birth explains their increased susceptibility to infections, and thus the importance of the passive transfer of maternal antibodies from their mothers' either via the placenta or colostrum for protection against diseases in the early stages of life.

Immune Senescence

Immunosenescence or age-related immune dysfunction refers to the inability of an aging immune system to produce an appropriate and effective response to challenge (Targonski et al., 2007). This decline in immunity can be attributed to multiple immune-specific factors that occur as an individual ages, such as the reduction in haematopoietic tissue potential, the involution of the thymus, and repeated exposure to pathogenic stress.

The overall capacity for renewal of HSCs decreases with age as does the amount of haematopoietic tissue in the bone marrow (Weiskopf et al., 2009). As most immune cells ultimately derive from HSCs, these age-associated changes have a significant effect on the body's defence mechanism (Linton and Dorshkind, 2004). This fall in haematopoietic potential is thought to be due to the shortening of telomeres that occurs with each DNA replication event. Fewer progenitor B cells are created and thus less of these cells are able to go through the various differentiation steps to become naive B lymphocytes and further onto memory cells. In contrast, progenitor T cells are less affected by HSC aging (Weiskopf et al., 2009) however, the involution of the thymus with age, leads to a skewing of the T cell repertoire, a decreased ability to activate naïve T cells and inability to generate robust memory responses (Ponnappan and Ponnappan, 2011). Ramifications of this age-induced lymphopaenia cause lymphocytes to proliferate, increasing memory but their ability to establish immunological memory in response to de novo antigens is reduced. Cytokine production by T lymphocytes become impaired and key surface markers are altered (Simon et al., 2015), negatively impacting on the process of antigen presentation.

The most significant cause for the drop in immune status is due to the reduction in T lymphocyte education and repopulation as a result of thymic involution. The thymus is a primary lymphoid organ vital to maintain homeostasis of the peripheral immune system through the production of a diverse repertoire of immunocompetent T cells (Aw and Palmer, 2011). Thymic involution occurs in all mammalian species, defined by the replacement of thymic parenchymal tissue with

fat and the resulting gradual decline in thymic output. This occurs as early as the first year after birth in humans though it can vary according to the longevity of the animal species and/or breed (Holder et al., 2016). Progenitor T cells migrate from the bone marrow to the thymus where they undergo extensive education and differentiation to turn into competent naïve T cells before exported to the periphery. These naïve T lymphocytes may subsequently become activated through antigen presentation and even further differentiate into memory cells (Lynch et al., 2009) to fend off invaders. Consequences of thymic involution are thus linked to alterations in the phenotype and function of T cells which broadly contribute to the clinical signs of immunosenescence (Aw and Palmer, 2011).

Constant and repeated onslaught to the exposure of antigenic insults throughout an individual's lifetime is responsible for the further decline in mature lymphocyte populations in the host as they age. Chronic activation of T lymphocytes due to lifelong viral persistence in immune-competent hosts influences and shapes the T cell repertoire (Ponnappan and Ponnappan, 2011). Any antigenic stimulus encountered by naïve lymphocytes result in the production of memory cells to cope with the stressor. However, these same, repeated physiological responses at the same time to keep latent infections at bay can lead to the progressive accumulation of expanded clones of memory cells which figuratively saturates the 'immunological space' (Franceschi et al., 2000) and exhausts pools of naïve lymphocytes. Excerbated by the involution of the thymus, the shortage in naïve lymphocytes is directly responsible for the increased susceptibility to infection by other infectious pathogens as well as non-infectious diseases where immunity and inflammation have an important role (Franceschi et al., 2000).

Besides the immune system related causes mentioned earlier, predominantly affecting the adaptive immunity in a greater scale to the innate response, general age-related changes such as the accumulation of reactive oxygen species (ROS), alteration in deoxyribonucleic acid (DNA) repair and telomerase attrition also contribute to the decline in immune response (Ponnappan and Ponnappan, 2011), affecting both the innate and adaptive systems. ROS come about as a negative side effect to the metabolism of oxygen, vital for life in aerobic organisms. It is implicated in the deleterious effects of aging. Production and accumulation of ROS together with telomere attrition and altered gene regulation due to inadequate DNA repair can result in dysfunctional proteasomes, altered autophagy and proteostasis (Ponnappan and Ponnappan, 2011) all of which result in the degeneration of the immune system in the ageing individual.

Conclusion

In summary, as the aging process advances, immunity weakens due in large part to the deterioration of lymphocytes, especially T cells, of the adaptive immune responses in terms of quantity and quality of protection. Thymic involution is a large contributor of the decline in function of T cells and thus can be seen as a prominent regulator of ageing. A complete understanding of the mechanisms involved in the aging immune system can have a role of practical applicability. Contributors to age-associated immune dysfunction can be used as biomarkers of ageing such as low telomere lengths, accumulation of DNA damage, as well as mutations to T cell surface receptors and more.

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