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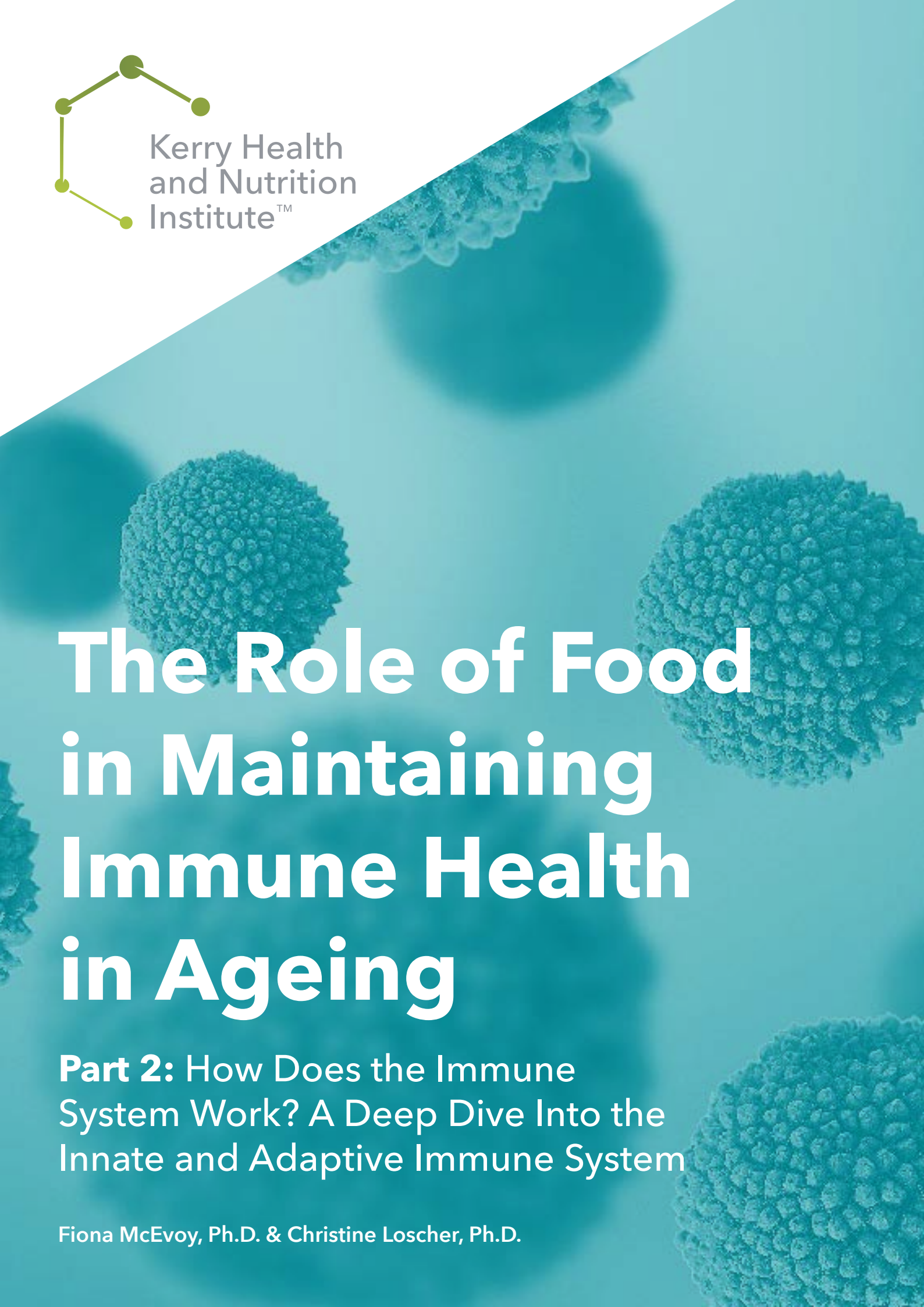


The Role of Food in Maintaining Immune Health in Ageing

Part 2: How Does the Immune System Work? A Deep Dive Into the Innate and Adaptive Immune System

Fiona McEvoy, Ph.D. & Christine Loscher, Ph.D.

What Does the Immune System Do?

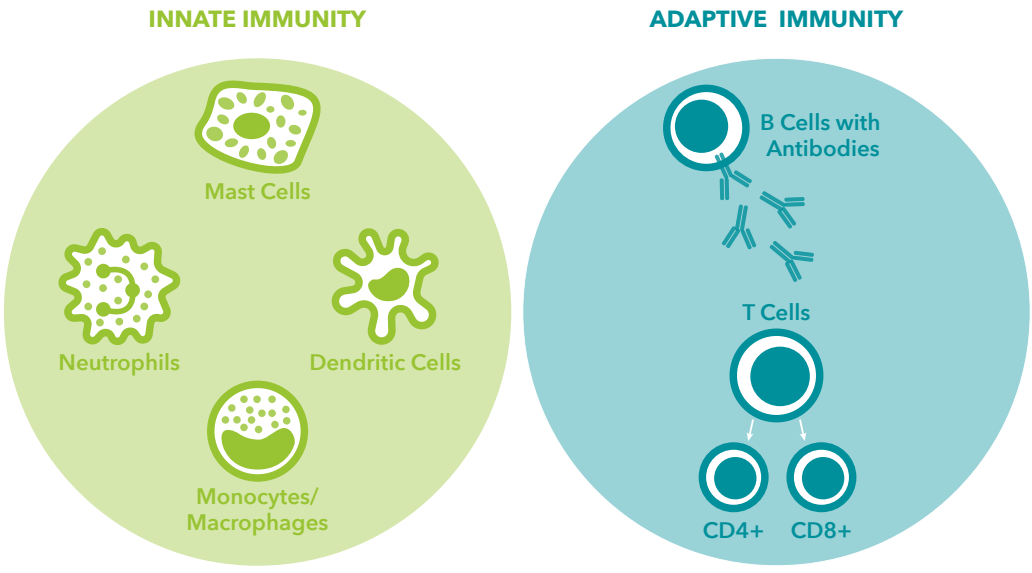
The immune system is a collection of cells, tissues and organs that has evolved to defend against dangerous pathogens and maintain homeostasis within an organism. The immune system maintains a constant surveillance against harmful bacteria and viruses, and has the ability to combat both foreign invaders and abnormal endogenous factors such as cancerous cells.

There are two branches of the immune system broadly divided into the innate and adaptive systems [4]. The innate immune system represents the rapid first line of defence against invading pathogens and is present in all multicellular organisms. Initial protection is provided by physical barriers to entry such as the skin and epithelial linings of the respiratory, gastrointestinal and mucosal systems. If a breach of these barriers occurs, cells of the innate immune system including monocytes, macrophages and neutrophils attempt to prevent invasion by means of inducing inflammation, phagocytosis of pathogens, release of lytic enzymes and activation of complement pathways [5].

The immune system maintains a constant surveillance against harmful bacteria and viruses

During these processes, dendritic cells (also known as antigen-presenting cells) engulf a portion of the antigen and migrate to the lymph nodes where they interact with, and activate T lymphocytes to initiate an adaptive immune response. The adaptive immune response is antigen specific and can initially take between four and seven days to develop. However, due to immunological memory, subsequent exposure to the same pathogen results in much quicker immune responses.

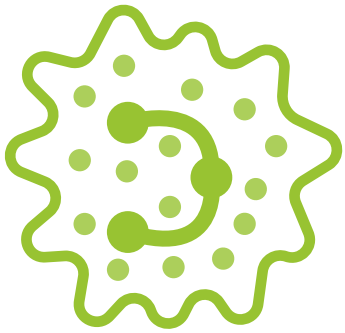
There are a number of different T cell populations whose activation depends on the type of pathogen encountered[6]. CD8+ cytotoxic T cells are very important for immune defence against intracellular pathogens and for tumour surveillance. CD4+ T helper cells (of which there are many varieties) play a major role in instigating and shaping adaptive immune responses via the secretion of various cytokines[7]. Furthermore, B lymphocytes (B cells) are responsible for producing antibodies that target extracellular pathogens.



CELLS OF THE INNATE & ADAPTIVE IMMUNE SYSTEMS

The Innate Immune System

Neutrophils



Neutrophils

Neutrophils are the first white blood cells recruited to sites of acute inflammation, in response to chemotactic cues such as IL-8, produced by stressed tissue cells and tissue-resident macrophages. Neutrophils constitute the primary immune defence against rapidly dividing bacteria, yeast and fungal infections, deploying microbicidal (i.e. destroys microbes) mechanisms including the generation of reactive oxygen and nitrogen species and the release of proteolytic enzymes and microbicidal peptides.

The appropriate initiation and resolution of their inflammatory responses is crucial to the clearance of infections and the prevention of non-specific tissue damage leading to chronic inflammatory disease.

Neutrophils show an age-related decline in most aspects of their microbicidal functions

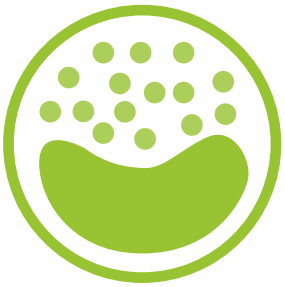
AGE RELATED DECLINE

Neutrophils constitute the largest population of white blood cells in humans and mice, and to date there has been no age-related decline in numbers observed[14]. However, neutrophils do show an age-related decline in most aspects of their microbicidal functions including chemotaxis, phagocytosis of microbes and generation of superoxide in response to stimulation by soluble host and bacterial factors [15,16].

The reductions in chemotactic and phagocytic ability observed in neutrophils from older donors would result in a delayed neutrophilic response to bacterial invasion, allowing rapidly dividing bacteria to establish a stronger core of infection. Inefficient chemotaxis also has the ability to increase tissue damage because neutrophils secrete proteases such as elastase to aid their migration through tissues; this is thought to extend inflammation and impair resolution of inflammation in older adults [14].

Neutrophils are the shortest-lived blood cells and their life span is extended at sites of infection by survival signals provided by cytokines (e.g. GM-CSF) and bacterial products (e.g. LPS). The age-associated reduction in neutrophils' ability to respond to survival signals, specifically GM-CSF, will result in compromised removal of microbes and thus extend the time to resolve the inflammation [17].

Monocytes / Macrophage



Monocytes/ Macrophages

Monocytes originate from myeloid stem cell progenitors and differentiate into macrophages with specialised functions depending on their location within the body [18]. Macrophages are specialised cells involved in the detection and destruction of bacteria and other harmful pathogens via phagocytosis and production of reactive oxygen and nitrogen species. They are also capable of releasing a vast range of cytokines and chemokines that are essential for the initiation and propagation of the inflammatory process [19].

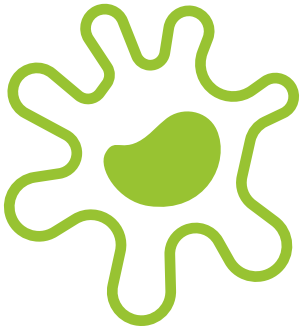
Macrophages are able to detect products of bacteria and other microorganisms using a system of pattern recognition receptors known as Toll-like receptors (TLRs). The TLRs are a family of invariant pattern recognition receptors with specificity for highly conserved portions of pathogens; 11 human TLRs have been identified to date. TLR activation results in both proinflammatory cytokine response via NF-κB-dependant pathway and the upregulation of type I IFN and IFN dependant genes [5].

The innate immune system is the rapid first line of defence against invading pathogens

There is conflicting data surrounding the effect of ageing on macrophage chemotaxis and phagocytosis with some studies showing decreases while others report the opposite [20]. There is now however a large body of data to support the theory that ageing alters cytokine secretion by macrophages in response to TLR stimulation. Age-associated decreases in LPS-induced (activating TLR4) IL-1β, IL-6 and TNF-α have been reported in mouse models [21,22] and a more generalised reduction in cytokine production in response to activation of TLR 2, 3, 4, 5, 6 and 9 was observed in macrophage from aged C57BL/6 mice [23]. Human studies of TLR function have also revealed age-associated declines in cytokine production with older subjects showing reductions in TLR1/2 induced IL-6 and TNF-α production in monocytes [24]. This functional defect in cytokine production was strongly correlated with a decrease in surface expression of TLR1 on the surface of monocytes from old compared with young individuals, and an age-associated decrease in TLR4 expression was also reported. Reduced TLR function and expression on monocytes and macrophage will compromise an individual's ability to both detect and eliminate harmful pathogens, thereby prolonging the duration and increasing the severity of infection.

Results from these studies would seem to contradict or question the observation of a heightened proinflammatory milieu in older individuals with higher circulating levels of cytokines such as IL-1β, IL-6 and TNF-α and proinflammatory markers such as C-reactive protein commonly referred to as 'inflamm-ageing' [13]. However, serum levels of cytokines might reflect production from a variety of tissue types. For example, although monocytes/macrophages are a major source of IL-6, it is also produced by endothelial cells, adipocytes, muscle cells, stromal cells and other cell types that are susceptible to the ageing process [25].

Dendritic Cells (Antigen-Presenting Cells)



Dendritic Cell

Antigen presentation is a critical event in the regulation of antigen-specific immune responses. Antigen-presenting cells (APCs) engulf, process and present pathogen-associated antigens on major histocompatibility complex (MHC) molecules recognised by T cells resulting in antigen-specific immune responses and long lived immunity [26]. APCs include macrophages, B cells and dendritic cells (DCs), however it is DCs that act as the main interface between the innate and adaptive immune system. DCs can be classified into two subsets: myeloid DCs (mDCs) and plasmacytoid DCs (pDCs) that are of a lymphoid lineage. Both mDCs and pDCs originate from a common DC precursor that originates from hematopoietic stem cells in the bone marrow [18]. During pathogen invasion, DCs detect intruders via pattern recognition receptors (e.g. TLRs), capture antigens and quickly migrate to the draining lymph nodes where they will present antigen to T cells via MHC molecules and elicit a specific immune response.

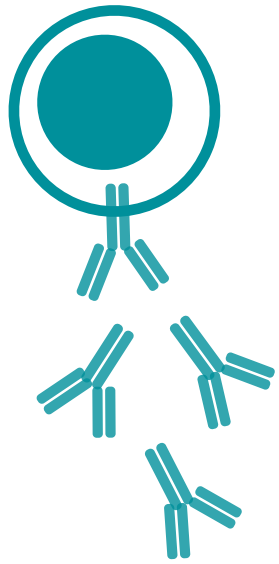
Antigen presentation is a critical event in the regulation of antigen-specific immune responses

One of the potential mechanisms by which ageing impacts the overall function of DCs is by alterations in number or distributions of this cell. However, there has been conflicting data reported to date. Significantly lower numbers of mDCs and pDCs have been observed in the frail elderly when compared to both healthy young and healthy elderly subjects [27].

Other studies have found no significant differences between peripheral mDCs and pDCs between young and elderly subjects [28] while another observed a reduction in mDCs with age [29]. Studies have generally found impairments in inflammatory responses of DCs, principally to TLR activation. Reduced IFN responses of pDCs from aged individuals to both the influenza and West Nile virus have been reported [30,31]. This is of note as the influenza virus is known to induce higher mortality in older people [8] and older people exhibit more severe infection following contact with West Nile virus [32].

The Adaptive Immune System

B Cells



B Cells with Antibodies

B cells are derived from pluripotent haematopoietic stem cells in the bone marrow. Their main function is the production of specific antibodies in response to a specific antigen and this function is critical for an effective response against extracellular bacterial infections and for vaccinations.

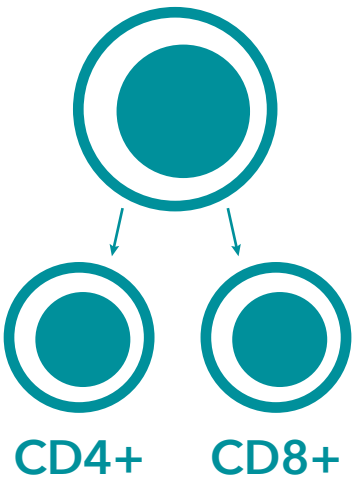
Highaffinity-specific antibodies are generated by somatic hypermutation of immunoglobulin (Ig) genes in the germinal centre of lymphoid tissue, after which professional antibody secreting plasma cells migrate to the bloodstream [33]. Large amounts of antibodies are then secreted into circulation and provide defence against harmful pathogens through a number of processes. They can bind directly to antigens, effectively coating the surface of the invader, in order to prevent pathogens from entering or damaging healthy body cells.

ANTIBODIES STIMULATE THE IMMUNE SYSTEM

Antibodies can also stimulate other parts of the immune system (e.g. complement proteins) to destroy the pathogens. Furthermore, they can mark pathogens through a process known as opsonisation so that the pathogens can be identified and neutralised by other immune cells. Memory B cells are also generated, which provide immunological memory in case of subsequent infection with the same pathogen.

The total number of B cells has been reported to diminish with ageing [34]. Additionally older people present with a decrease in the diversity of their B cell repertoire characterised by an increase in memory B cells and a decrease in naïve B cells [35,36]. Consistent with the change in B cell numbers and subsets, antibody production is also affected by age. In response to vaccinations, older persons present a delayed response seen as a reduced clonal expansion of plasma cells. This finding correlates with decreases in Ig production and these Ig cells have lower affinities toward their antigens [37]. Additionally, when a primary antibody response is required in the presence of novel antigens, the elderly display a delayed response with lower levels of high affinity antibodies [38]. This would in part, explain the longer duration and increased severity of infections experienced by the elderly population.

T Cells



T Cells

Most of the lymphocytes in the blood are T cells. While B cells mature in the bone marrow, T cell precursors migrate to and mature in the thymus. T cells are characterised by the presence of T-cell receptors (TCRs) and can be categorised into two main subsets by their surface expression of either CD4 or CD8 [6]. CD4+ cells, which recognise antigens presented on class II major histocompatibility complex (MHC) are mainly regulatory cells, whereas CD8+ cells are cytotoxic and recognise antigen presented on class I MHC molecules. Both functions are of vital importance for both the adaptive and innate immune responses. CD4+ T cells are also referred to as T helper (Th) cells, as they assist other white blood cells in immunologic processes, including maturation of B cells into plasma cells and memory B cells, and activation of cytotoxic T cells and macrophages.

Th cells can be further categorised into different subsets (e.g. Th1, Th2, Th17, Treg) based on production of signature cytokines [7]. CD8+ T cells (also known as cytotoxic T cells) are vital for immune defence against intracellular pathogens and for tumour surveillance. CD8+ T cells kill infected and malignant cells through the secretion of pro-inflammatory cytokines, the release of toxic granules called perforins and granzymes, and through the use of Fas/FasL interactions [39].

Immunological memory is part of the adaptive immune system and provides better protection against repeat infections

Similar to B cells, the total number of naïve T cells decreases with age. T cells develop in the thymus, which decreases with age due to age-related changes that affect both T-cell progenitors and the thymic microenvironment [40]. This decline affects CD4+ and CD8+ cells differently with a better preserved population of naïve CD4+ cells and greater decline in CD8+ cells (Ferrando-Martinez et al. 2011). Alterations in the CD8+ T cell compartment are some of the best characterised age-related changes in the immune system. These cells tend to undergo oligoclonal expansion with age and, as such the CD8+ T cell repertoire becomes increasingly skewed towards previously encountered antigens [42,43].

There is an association between the increase in the prevalence of CD8+ T cell oligoclonal expansion and cytomegalovirus (CMV) infection status, which establishes life-long latent infection [42]. This oligoclonal expansion can also limit the ability of the CD8+ T cell population to respond to newly encountered pathogens such as emerging strains of the influenza virus, which could explain the increased morbidity and mortality rates associated with influenza infection in the elderly. Activation of both naïve and memory T cells is a complex process that requires the intervention of co-stimulatory molecules such as CD28 after the binding of the TCR to MHC molecules [44]. Binding of CD28 to its co-receptor results in a potent activation stimuli for T cells and although this activation is not impaired with ageing, the expression levels of CD28 in both CD4+ and CD8+ T cells decreases [45]. This is consistent with a decreased naïve T cell pool and the accumulation of highly differentiated T cells.

Fiona McEvoy, Ph.D. completed her postdoctoral studies at Dublin City University, where she focused on identifying novel compounds that can modulate the immune system to provide therapeutic benefits using in vitro and in vivo models.

Christine Loscher, Ph.D. is a Professor of Immunology at Dublin City University. She is also the Lead Investigator of the Immunomodulation Research Group and has developed significant expertise in commercial research and industry engagement. She has secured over €4.5M in external funding for her research.

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