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In this article...

- Age-related changes to the innate and adaptive immune responses
- Thymic involution and immunosenescence
- Decreased production and impaired function of ageing immune cells

Anatomy and physiology of ageing 9: the immune system

Key points

Almost all components of the immune system are adversely affected by age

One of the earliest and most drastic changes in the immune system is thymic involution

The innate immune response, provided by mechanical barriers, and cells with phagocytic and killing abilities, is blunted

The weapons of the adaptive immune response, T cells and B cells, undergo a decline in numbers and function

Better vaccines, a healthy population of gut microbes, vitamin intake, zinc supplementation and exercise can support the ageing immune system

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Abstract With advancing age, the body's ability to respond to infection declines, and recovery from injury or microbial attack becomes delayed or ineffective. This is called immunosenescence. The innate immune response, the acquired immune response and the inflammatory response are all blunted, and the immune system becomes less able to mount a rapid and complete defence against invading pathogens. Ageing also means older people respond less well to vaccines and are more prone to autoimmune conditions. This is the ninth article in an 11-part series on the effects of ageing on the systems of the body.

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Survival depends on the body's ability to protect itself against environmental dangers, harmful substances and pathogens. It does this using non-specific, natural (innate) defences such as the skin, secretions, immune cells and chemicals. The innate immune system is bolstered by the inflammatory response (Box 1), which increases blood flow to damaged areas and encourages phagocytic leucocytes to enter injured tissues and engulf pathogens. The non-specific immune responses are complemented by acquired (adaptive) immune responses, which develop more gradually but more robustly, targeting individual pathogens and ridding the body of malignant cells.

Almost all components of the immune system are adversely affected by ageing, resulting in an overall decline in immunocompetence. The system becomes less able to mount an effective response and the mechanisms normally invoked to get rid of a foreign agent are disrupted; this decline is called immunosenescence. The innate defences change profoundly, but the adaptive defences undergo an even more severe age-related deterioration.

Innate immune response

The innate immune system has two lines of defence:

- The skin, and the epithelial and mucosal linings of internal organs;
- Non-specific white blood cells (leucocytes) and secreted molecules, including antimicrobial factors such as defensins, which can pierce the membranes of pathogens.

If a pathogen breaches the exterior, first-line barrier, the second-line internal defences come into play. The hallmark of the second line of innate defence is inflammation (Box 1). The innate defence also depends heavily on cells that can phagocytise pathogens – neutrophils, monocytes and macrophages.

Skin, mucous membranes and eye lashes

The skin contains keratin, a waterproof and microbial-resistant protein. Lactic

acid secretions allow the skin to maintain a slightly acidic environment (pH5.5) and sebaceous and sweat glands produce secretions that can inhibit bacterial growth.

With age, skin secretions diminish; the skin becomes thinner, drier and less elastic, and therefore more prone to cuts and abrasions through which pathogens can enter the body. Medical devices such as intravenous cannulas provide skin breaches, so should only be used when absolutely necessary, removed as soon as possible, and accompanied by tight infection prevention and control measures.

Mucous membranes line cavities, tracts and structures throughout the body. The mechanical protection provided by their tough epithelium is reinforced by the production of mucus that traps particulate matter and pathogens. With advancing age, the integrity of the epithelial barrier and mucosal immune response are compromised (Man et al, 2014).

Eyelashes keep debris out of eyes; like hair, they grow through specialised follicles, but this process slows down with age, and eyelashes become thinner.

Cells of the innate immune system

Neutrophils

The primary immune defence against rapidly proliferating bacteria, yeast and fungi are phagocytic neutrophils, which can destroy pathogens by rapid generation of potent reactive oxygen and nitrogen species, as well as extrude neutrophil extracellular traps. Neutrophils are also important in wound healing: they arrive at the wound site within minutes of an injury and continue to do so for several days.

With advancing age, the number of neutrophils remains constant but their function is affected (Solana et al, 2012); reduced phagocytosis (ability to ingest microbes) may lead to an accumulation of debris, while reduced chemotaxis (movement in response to chemical stimulation) means neutrophils take longer to reach the site of infection. Neutrophils secrete proteases to aid their migration through tissues: this also becomes less efficient with age. Tissue damage and inflammation are therefore more frequent and more severe in older people (Shaw et al, 2010).

Monocytes and macrophages

Monocytes are white blood cells located in the spleen and blood. They respond to inflammation by differentiating into antigen-presenting cells (APCs) such as macrophages and dendritic cells. Macrophages release a range of inflammatory mediators, including cytokines and chemokines, playing a key role in the inflammatory process (Box 1). When they encounter invading microbes, they initiate inflammation – recruiting and activating other phagocytes. Macrophages are also key to wound healing, producing growth factors and secreting angiogenic and fibrogenic factors. With age, there is a sharp decline in the function of macrophages, and their phagocytic, killing and wound-healing capacities are reduced (Linehan and Fitzgerald, 2015; Solana et al, 2012).

Dendritic cells

Dendritic cells are antigen-presenting leukocytes found at the body's frontiers such as skin. They activate T-lymphocytes and play a pivotal role in the adaptive immune response (see below).

Natural killer cells

Natural killer cells (NKCs) are non-specific cytotoxic white blood cells involved in early defence. Known as the pitbulls of the immune system, they recognise and eliminate a variety of virus-infected cells and malignant cells by direct contact. Their ability to kill is seen as a biomarker of healthy ageing, and low NKC activity is associated with the development of diseases and infections. Absolute numbers of NKCs increase with age but their cytotoxic abilities decrease (Shaw et al, 2010). Age-associated alterations in NKC function may result in part from changes in zinc homoeostasis; there is some evidence zinc supplements improve NKC function (Mariani et al, 2008).

Adaptive immune response

The main weapons of the adaptive immune system are B and T cells (lymphocytes), which create and acquire immunity to specific antigens. Since the adaptive immune response is antigen-specific, it needs to be primed by initial exposure, so the adaptive immune response usually kicks in a few days after the innate immune response.

The thymus

Precursors of B and T cells are formed in the bone marrow, but T cells mature into immunocompetent lymphocytes in the thymus gland. Located just above the heart, this lymphoid organ is large and active in early childhood and then rapidly decreases in size, at a constant rate, until middle age. Atrophy (shrinking) of the thymus is one of the earliest and most drastic changes in the immune system and this is thought to play a major role in immunosenescence. It results in a gradual decrease in the output of naive T cells, which essentially stops between 50 and 60 years of age (Muller and Pawelec, 2015). The production of various immunoregulatory hormones that differentiate T and B cells also decreases: some are no longer detectable in the plasma of people over 60.

One role of the thymus is to mature T cells that have not yet been exposed to antigens. These 'naive' T cells are quiescent, and will only become active when exposed to a foreign antigen. Another role of the thymus is to 'educate' T cells to recognise self-antigens, so that they do not mount an attack against self-cells and tissue. Here, maturing T cells are checked to ensure that they do not strongly respond to self body proteins. Due to thymic atrophy, this 'thymic education' is impaired by ageing, which may partly explain why we have more autoantibodies as we age.

T cells

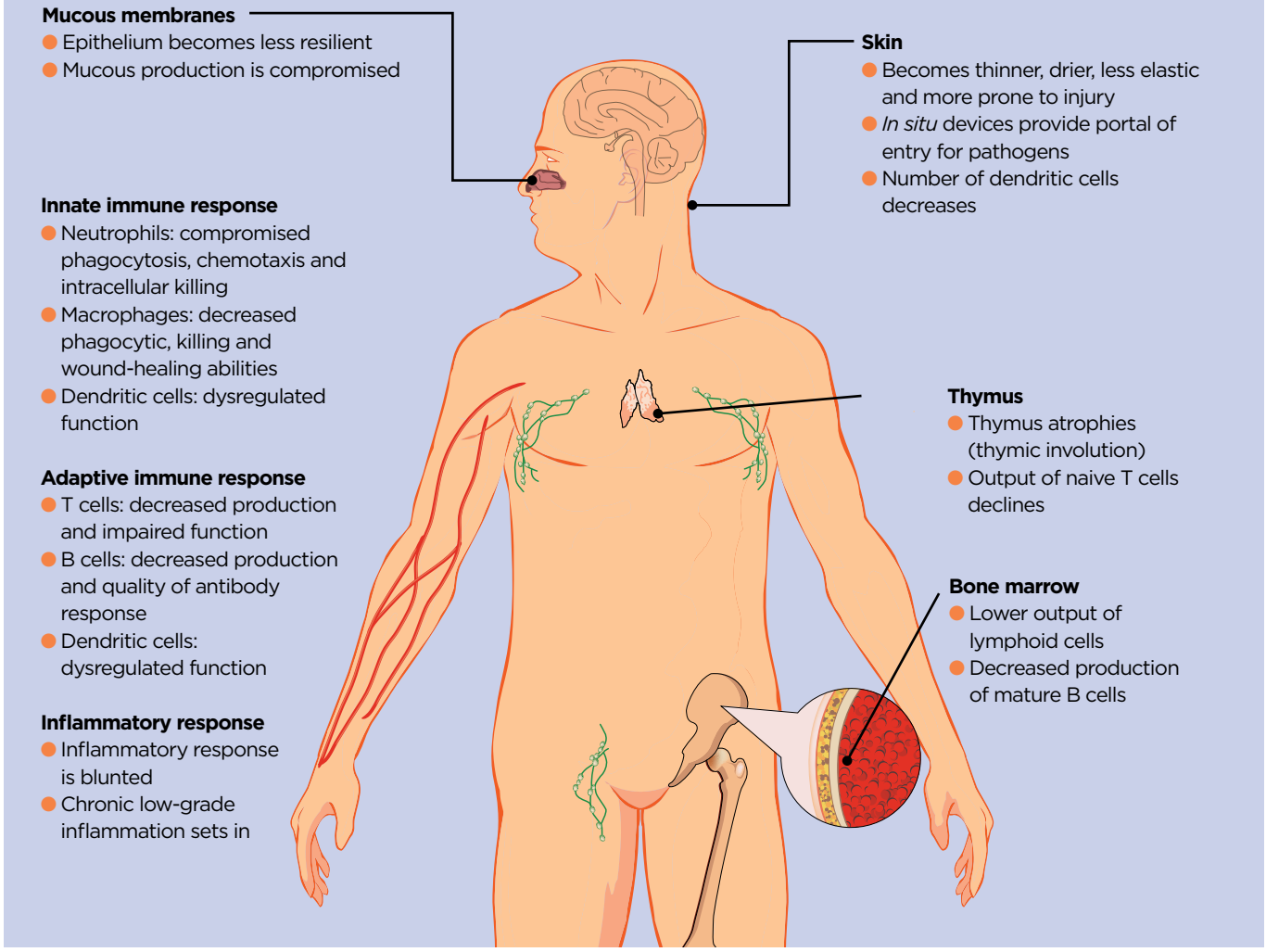
Matured naive T cells are exported to the secondary lymph organs (lymph nodes and spleen), where they are more likely to encounter foreign antigens. T cells make up 65-85% of blood lymphocytes and circulate through lymph, blood and back to lymph nodes once a day, therefore

Box 1. Inflammation and inflammageing

Inflammation isolates and protects the body from further injury and the spread of invading pathogens. Histamine release causes an increase in blood flow to the injury site, and prostaglandins allow white blood cells and plasma to migrate out of the capillaries. A cascade of complement proteins in the plasma kick-starts this physiological process, which results in the classical symptoms of inflammation: redness, heat, swelling and pain.

With age, in the presence of infection, both the complement pathway and the activation of inflammation are reduced (Navaratnarajah and Jackson, 2017). Ageing is also associated with a long-term, continuous state of low-grade inflammation (inflammageing), which can trigger other pathological mechanisms. This low-grade systemic inflammation is considered the primary risk factor for major long-term conditions in older people (Isobe et al, 2017).

Fig 1. **Age-related changes to the immune system**



increasing their chances of encountering a variety of antigens. Once they have bound with an antigen, T cells proliferate and can differentiate into different types: cytotoxic T cells (which mediate the direct killing of target cells), helper T cells (which assist all other immune cells) and memory T cells (which remain dormant but will reactivate on re-exposure to the same antigen).

The activation of T cells depends on their interaction with APCs, which 'show' them the antigen. APCs include dendritic cells: with their wispy extensions, these will catch antigen, phagocytise it, and then enter a lymph node where they will present bits of their caught antigen to T cells.

Dendritic cells play a pivotal role in the adaptive immune response. Their age-associated dysregulation not only compromises anti-pathogen defence, but also wreaks havoc on general immunological function (Muller and Pawelec, 2015).

Older people have vast numbers of memory T cells, but almost no naive T cells, so they do not respond to new antigens as well as younger people. However, age-related loss of efficiency of the adaptive immune system is thought to be mainly due to a decline in T cell receptors caused by the cytomegalovirus (CMV) (Oishi and Manabe, 2016). This virus is highly prevalent in older people and associated with increased rates of vascular disease and overall mortality (Parry et al, 2016). The capacity of T cells to respond to infection is almost entirely absorbed by the CMV (Isobe et al, 2017), leaving older people vulnerable to other infections.

B cells

B cells originate and mature in the bone marrow and, like T cells, are activated by antigens. Once activated they become antibody-secreting plasma cells. Secreted antibodies (immunoglobulins) function by targeting extracellular pathogens and neutralising antigen. Some B cells become memory B cells, capable of remembering the antigen that triggered antibody production. Both B and T memory cells are on continuous patrol in the circulation (Marieb and Hoehn, 2016).

With increasing age, the bone marrow produces fewer mature B cells (Muller and Pawelec, 2015). Antibody responses to infectious agents – and vaccines – also tend to decrease due to deficient T-helper cells and intrinsic defects in B cells (Frasca et al, 2011). In older people, the humoral response is therefore of shorter duration and decreased specificity.

Vaccination

More than 90% of deaths from influenza occur in people aged over 65 (Katz et al, 2004). Older people are more susceptible to

infections, especially flu and pneumonia but also urinary tract infections. Hidden infections such as varicella zoster virus infection (which can cause shingles in people who have had chickenpox) and CMV are recurrent and can lead to life-threatening disease. In older people, shingles is associated with a transient risk of complications including stroke and myocardial infarction (Minassian et al, 2015).

Nurses must encourage older patients to have vaccines, even though it has been reported that influenza vaccination is only effective in 30-40% of the older population (Vu et al, 2002) and most vaccines are thought to be less efficient in older people (Weinberger and Grubeck-Loebenstein, 2012). An exception is the shingles vaccine, which works well in older people since it relies on existing memory T cells previously exposed to the varicella zoster virus, not new, naive ones.

A higher antigen dose and/or better adjuvants could help improve older people's response to vaccines (Derhovanessian and Pawelec, 2012); for example, the adjuvant MF59 (oil in water emulsion), given with the flu vaccine, helps stimulates antibody production (Salam et al, 2013). Another strategy could be to plan vaccination in middle age, before the onset of immunosenescence and while naive T cells are still able to produce memory cells.

Autoimmunity

To avoid autoimmunity, in which the immune system attacks the body's own healthy cells, the generation and education of immune cells must be closely controlled, but this may not work so well in older people (Muller and Pawelec, 2015). The number of autoantibodies increases substantially with age (Agrawal et al, 2012); studies have reported a higher prevalence of autoantibodies among healthy individuals aged 101-106 compared with people aged 26-60 (Candore et al, 1997), while autoantibodies such as rheumatoid factor were found in 79% of a sample of people aged over 100 (Andersen-Ranberg et al, 2004).

Dendritic cells are key players not only in the protection against pathogens, but also in the immune tolerance to self-antigens. They help maintain a balance. Normally they do not mount an immune response to circulating self-antigens in the periphery, and only mature and activate T cells if faced with a foreign antigen. However, infection or tissue injury may make dendritic cells mature inappropriately and lead to the development of autoimmune diseases (Agrawal et al, 2012).

Healthy ageing

There is currently a lot of interest in the gut bacterial population and its role in maintaining healthy metabolism and immune function. Restoring gut microbial balance by administering pre-biotics and probiotics appears to improve health and immunity in older people (Goronzy and Weyand, 2013); for example, the consumption of a drink containing *Lactobacillus casei* for four weeks had positive effects on the immune function of healthy older individuals (Dong et al, 2013).

Good nutrition in older people is crucial, since vitamin and mineral deficiencies impair the immune response. Medication can impair the absorption of vitamins and minerals, further reducing the body's ability to fight infection, and antihistamines, steroids and non-steroidal anti-inflammatory drugs can all impair the inflammatory response. Avoiding infection is crucial in older people: many die from infection or experience severe long-term effects, and an infection often marks the beginning of a downward spiral (Nazarko, 2009).

Finally, moderate exercise has been widely reported to help restore immunity (Simpson et al, 2012). Ranadive et al (2014) found that moderate aerobic exercise immediately before receiving the flu vaccine increased its efficacy in older women, and Irwin et al (2007) suggested that implementation of the Chinese martial art of tai chi alone induced a marked increase in virus-specific immune response. **NT**

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Anatomy and physiology of ageing – updated series

Article	Date
Part 1: the cardiovascular system	Feb
Part 2: the respiratory system	Mar
Part 3: the digestive system	Apr
Part 4: the renal system	May
Part 5: the nervous system	Jun
Part 6: the eyes and ears	Jul
Part 7: the endocrine system	Aug
Part 8: the reproductive system	Sep
Part 9: the immune system	Oct
Part 10: the musculoskeletal system	Nov
Part 11: the skin	Dec