Innate immunity: Definition and Importance

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Contents

INNATE IMMUNITY

DEFINITION AND IMPORTANCE

Overview of innate immunity in animals

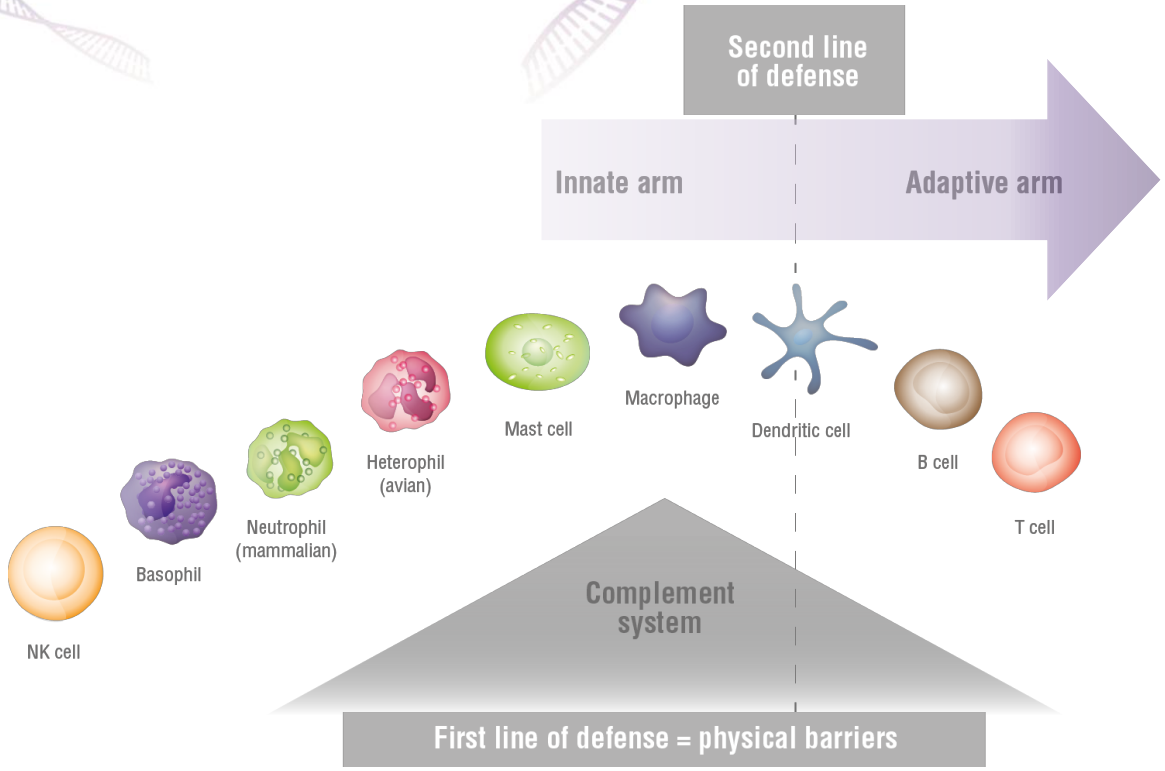
Once a pathogen has bypassed the animal's physical barriers and self-cleaning behaviors, it is recognized by the innate immune system, which triggers a broad immune response to combat infection. This innate response is non-specific and rapid, can affect a wide range of pathogen types, and also triggers the development of subsequent adaptive immunity.

The innate immune system acts early to contain infection

The immune system is the body's defense against invading pathogens. Given that removing pathogens from the body is essential for survival, it is not surprising that there are multiple interacting layers of defense (Figure 1). The body's physical barriers provide the first level of protection and include the skin and also the body's 'self-cleaning' processes such as sneezing or coughing. However, physical barriers cannot be completely effective and sometimes pathogens may overcome them. For this reason animals possess an immune system comprising a network of cells and molecules that can fight infection. It is the second line of defense, and can be thought of as having two phases of response, termed the innate and adaptive immune response.[1]

An animal's innate immunity is responsible for attempting to block pathogens from replicating before they can cause disease. Innate immunity is activated immediately after a pathogen penetrates the physical barriers and provides a non-specific response (innate immune response) that acts against a broad range of different pathogens. The innate immune system is complex and comprises biochemical and cellular pathways whose function is to recognize and actively remove invading pathogens, and to activate adaptive immunity.[1,2] Innate immune cells recognize pathogens by detecting markers on them, which triggers the secretion of signaling molecules that attract other immune cells to help combat the infection. This is known as inflammation. Each infection is treated in the same manner and innate immune cells do not adapt their response once a pathogen has been encountered; there is no immunological memory of that pathogen.[1,2]

Figure 1. The animal immune system defends against infection[3]



NK, natural killer.

Adaptive immunity relies upon innate immune stimulation

A crucial role of the animal's innate immune system is the activation of further immune responses, specifically, adaptive immunity – without stimulation by innate immune cells, there would be no highly specific, long-lasting adaptive immune response (Table 1).

Antigen-presenting cells (APCs) are a type of innate immune cell, that includes phagocytes, such as dendritic cells. They can internalize pathogens and then present a fragment of the pathogen, known as an antigen, to adaptive immune cells. The APC displays the antigen, along with costimulatory molecules, on its surface. Adaptive immune cells, such as T and B cells, can only recognize presented antigen. The APC costimulatory molecules allow the T or B cells to become activated; once activated they proliferate, producing many T and B cells that all recognize the same antigen (Figure 2).[4]

The adaptive immune system takes a few days or even weeks to become effective and provides a highly specific response, meaning it has the ability to recognize specific foreign antigen. Although it develops more slowly, once an adaptive response to a pathogen has been developed, the chances of that pathogen successfully escaping destruction are very low.[4]

Difference between the innate and adaptive immune system

One of the key differences between the innate and adaptive immune systems is that the adaptive immune system not only recognizes and destroys pathogens, but it also retains the memory of that encounter. Thus, if the animal is exposed to the same pathogen again, the adaptive immune system is able to respond more rapidly and more effectively to eliminate that pathogen. This is known as immunological memory.[4]

Table 1. The role of the innate immune response in animal health

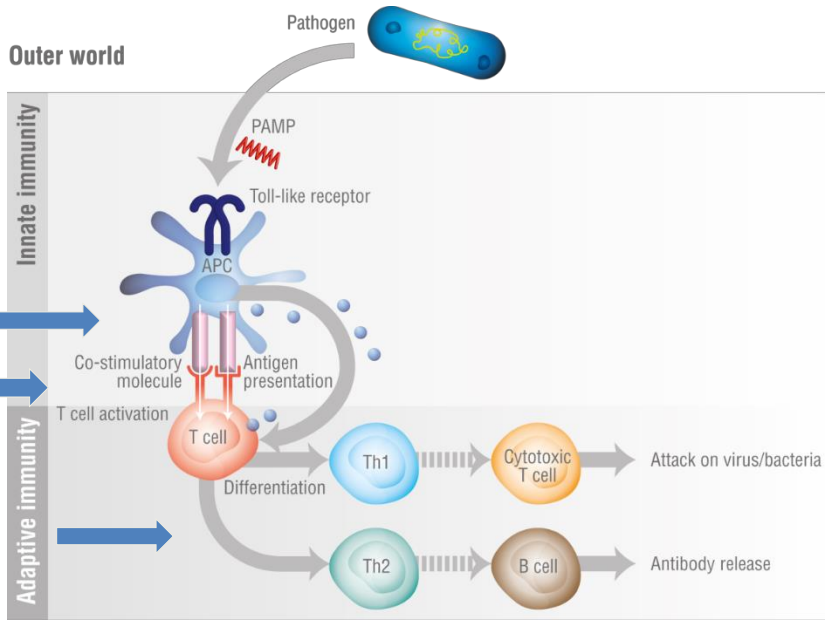
The innate immune system...	
...is fully developed at birth	Fights infection even in the absence of prior exposure to a pathogen
...is complex	Comprises biochemical and cellular pathways whose function is to recognize, and actively remove, invading pathogens, and to activate the adaptive immune response
...recognizes pathogens	Detects markers on pathogens and acts quickly to contain infection
...activates further immune responses	Without stimulation by innate cells, there would be no highly specific, long-lasting adaptive immune response

Figure 2. Adaptive immunity develops over time[5–7]

1. A pathogen is processed and presented by APCs

2. Additional costimulatory signals are provided by the APC

3. This leads to recognition by the adaptive immune system and the proliferation of T cells and B cells



Activation of the adaptive immune system

APC, antigen-presenting cell; PAMP, pathogen-associated molecular pattern; Th, T helper.

Cells and molecules of the innate immune system

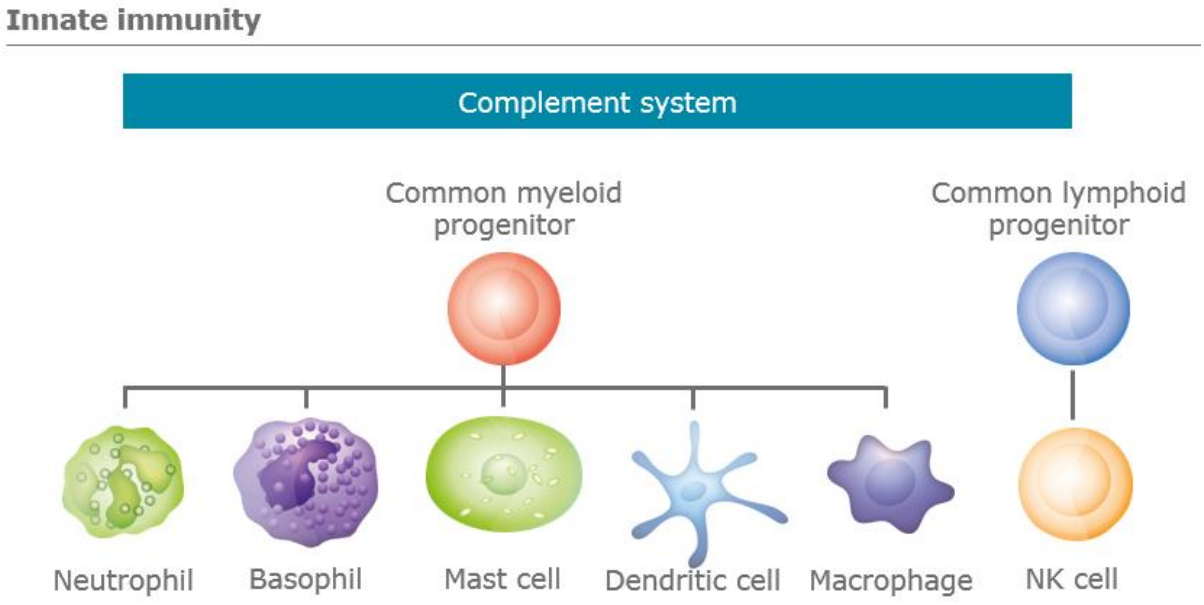
Toll-like receptors allow cells of the innate immune system to detect pathogens

The innate immune system consists of a network of cells and molecules that work together to fight off invading pathogens. This includes dendritic cells, macrophages, mast cells and neutrophils – all of which are phagocytes (Figure 3). A phagocyte is a type of innate immune cell that ingests and degrades pathogens. In order to do this, phagocytes express receptors that detect pathogen-associated molecular patterns (PAMPs). PAMPs are molecular structures that are not present in vertebrates (e.g. mammals and birds) but are found on microorganisms. The presence of PAMPs allows innate immune cells to recognize pathogens as 'non-self'.[8]

Toll-like receptors (TLRs) are a family of pattern-recognition receptors that detect PAMPs. They are located on the surface of innate immune cells, or within endosomes inside the cells. Each TLR, e.g. TLR9, recognizes a different PAMP. The binding of a PAMP to a TLR sends a danger signal that begins a biochemical cascade to alert other immune cells to the presence of a pathogen. TLRs are crucial to the first line of defense against bacterial infections, as well as viral and fungal pathogens, playing a vital role in microbial sensing.[9]

As pathogenic DNA has a different structure to vertebrate DNA, it acts as a PAMP, allowing the animal's immune system to recognize it as foreign. DNA sequences called CpG motifs are unmethylated in pathogens, while in vertebrates they have a chemical modification known as methylation.[10] Therefore, when TLRs encounter unmethylated CpG motif DNA, it signals to the cell that a pathogen is present. There are species differences with respect to TLRs, for example, in cattle TLR9 recognizes unmethylated CpG DNA, whereas in poultry TLR21 performs this function.[11–13]

Figure 3. The innate immune system in more detail[14]



NK, natural killer.

Immune signaling

Cytokines are proteins that send signals between cells to coordinate an immune response. When a TLR is activated by binding to a PAMP, a signaling cascade sends a message to the cell's nucleus to turn on certain genes that produce cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1 and IL-6. These cytokines are then secreted by the cell that detected the PAMP, for example, neutrophils, monocytes, macrophages, mast cells, or dendritic cells.[9,15,16] The cytokines can be detected by other immune cells, including nearby macrophages, neutrophils or dendritic cells, and also non-immune cells, such as endothelial cells.[15] Cytokines instruct immune cells to fight the invading pathogen and are produced in response to stimuli that signal infection, e.g. PAMPs, antigens and antibodies. They are short-lived but can act on many different cellular targets. Cytokines modify cell behavior by inducing signaling changes and altering gene expression. They may have stimulatory or inhibitory effects, depending on the cytokine, and they often induce or regulate the production of other cytokines. Some important cytokines secreted by macrophages are given below:[17]

- TNF-α acts on vascular walls to allow entry of cells, complement and antibodies into the tissues to help contain infection
- IL-1β helps the immune cells to leave the blood and enter the tissues, and it also activates cells of the adaptive immune system that are called lymphocytes
- IL-6 activates lymphocytes and increases production of antibodies

Together these three cytokines contribute to the acute phase response, during which the liver synthesizes acute phase proteins. These have a similar action to antibodies but unlike antibodies, which are highly specific for a particular antigen, they can target a range of PAMPs and by binding to them, make the pathogen easier for immune cells to detect.[17] IL-10 is an immunoregulatory cytokine, produced mainly by T cells but also by macrophages and DCs. Its effects include suppression of the proinflammatory cytokines mentioned above and suppression of innate and adaptive immune cells.[18]

The complement system and innate immunity

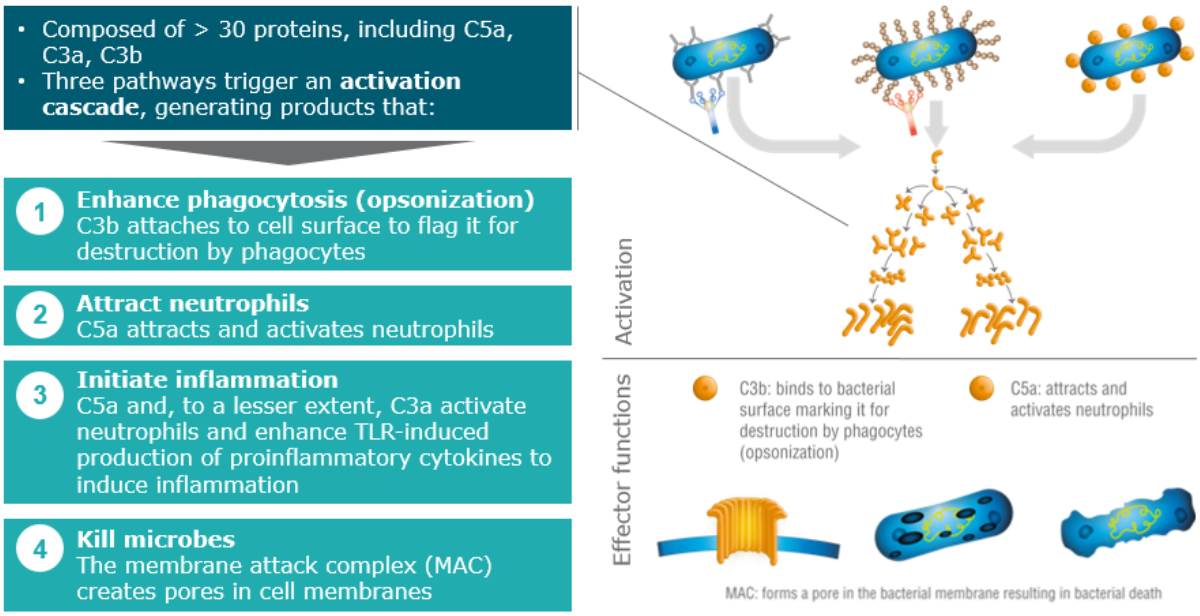
Complement is a system of interacting protein molecules that aids in the removal of pathogens from an animal and forms an important component of innate immunity. Its main role is to protect against infection, but it can also be involved in the regulation of inflammatory processes, the removal of damaged or altered cells, sending 'danger' signals throughout the body, and regulating adaptive immune responses.

It is composed of > 30 proteins, including C5a, C3a and C3b. Three pathways trigger an activation cascade and the pathogen surface is a key site where complement activation occurs. The three pathways converge and produce the same set of effector proteins that:

1) Enhance phagocytosis (opsonization) – C3b attaches to the cell surface of microorganisms to flag them for destruction by phagocytes;
2) Initiate inflammation – C5a and C3a attract and activate neutrophils and mast cells and enhance TLR-induced production of proinflammatory cytokines; and
3) Kill microbes – the membrane attack complex (MAC) creates pores in cell membranes to kill bacteria (Figure 5)

In addition to these effects, complement proteins plays a role in activating adaptive immunity. Complement can coat the surface of antigens and also of components from dying cells. As antigen-presenting cells express receptors for complement protein, these complement-coated antigens and dead cells are more easily picked up by phagocytes and disposed of.[19,20]

Figure 5. Complement system marks pathogens for destruction by phagocytes[20]



The immune response to infection

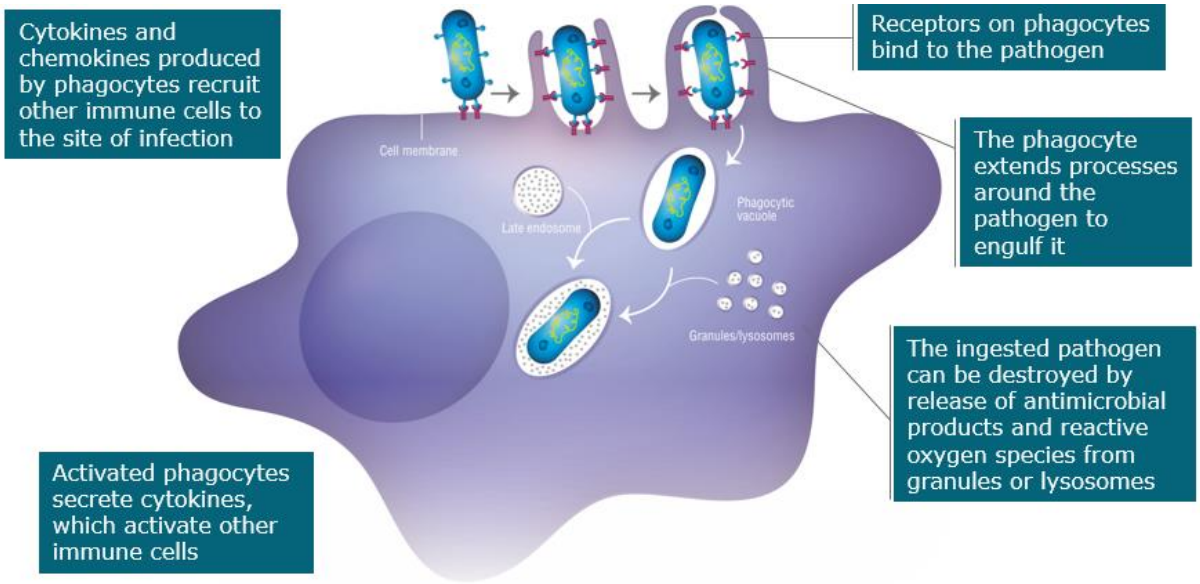
Pathogens are eliminated by phagocytes

As the most common site of entry of a pathogen into the body is the skin or mucosa, a type of phagocyte known as macrophages reside in the tissue below, acting as sentinels on the look out for invading pathogens.[21,22] Once identified, the next stage is to remove the infecting pathogen from the tissues so that it does not replicate and cause damage. There are many receptors on the phagocyte surface that enable it to discriminate between self-cells and pathogens.[21] When a pathogen is detected, the phagocyte extends itself around the pathogen, taking the pathogen into an internal compartment inside the phagocyte, in a process termed phagocytosis.[22]

Phagocytes produce a number of toxic products that kill ingested pathogens. Some phagocytes contain primary granules which release antimicrobial peptides and protease enzymes onto the pathogen, which have widespread activity against different pathogens. The pathogens are digested by these toxic products in the intracellular compartment, and the broken-down products are then released from the phagocyte. During phagocytosis, the phagocyte undergoes a period of increased oxygen consumption and during this time enzymes are activated to produce reactive oxygen species, which are also toxic to the ingested bacteria (Figure 6).[22,23]

Another consequence of the interaction between phagocytes and pathogens is that phagocytes become activated. This causes them to release cytokines, which signal to other immune cells.[22]

Figure 6. Phagocytosis is a receptor-regulated process and can trigger production of inflammatory mediators[24]



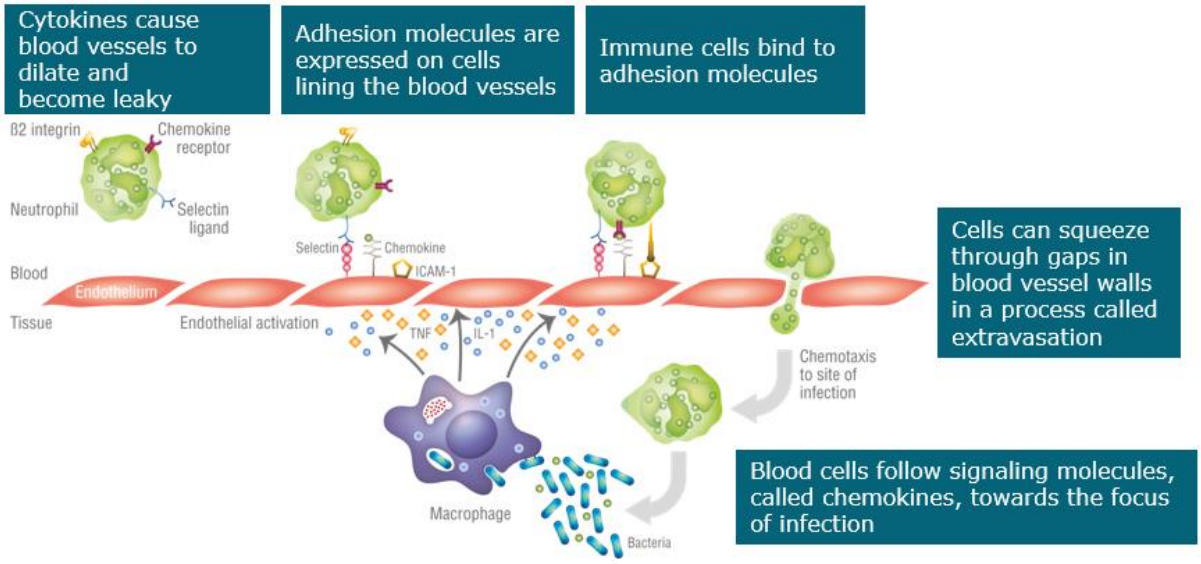
Activated macrophages initiate cytokine inflammation to recruit immune cells to the site of infection

As discussed in the section on cells and molecules of the innate immune system, the detection of PAMPs on pathogens by TLRs on phagocytes initiates a signaling cascade that results in the

phagocyte secreting cytokines.[9,25] Cytokines are responsible for the process known as inflammation, which helps more immune cells reach the site of infection in order to increase the strength of the immune assault against the infecting pathogen.[26,27] Cytokines move through the tissues and when other immune cells encounter the cytokines, they signal through the cell's cytokine receptors to modify cell behavior by causing changes in signaling and gene expression.[26,27] Cytokines can also cause changes to the cells that make up the blood vessel walls, known as endothelial cells. Blood vessels dilate and become leaky and express adhesion molecules on their surface. Immune cells bind to the adhesion molecules and then squeeze through the gaps in blood vessel walls to enter the tissues. Once in the tissues, immune cells follow a type of cytokine, called chemokines, which lead the cells to the focus of infection (Figure 7). This influx of immune cells to the site of infection produces the characteristic signs of inflammation; redness, swelling, heat and pain.[25–27]

Neutrophils arrive at the infection site first, followed by monocytes and immature dendritic cells (DCs). Once there, certain chemokines and complement proteins can cause activation of these immune cells. The activated immune cells are equipped to fight the infection through phagocytosis.[26]

Figure 7. The inflammatory response helps immune cells reach the site of infection[28,29]



Selectin and ICAM-1 are adhesion molecules. TNF and IL-1 are cytokines.
ICAM-1, intercellular adhesion molecule 1; TNF, tumor necrosis factor; IL-1, interleukin 1.

Interaction between innate and adaptive immunity

Dendritic cells link the innate and adaptive responses[30]

Dendritic cells (DCs) can carry out phagocytosis but they have additional functions and can be thought of as the bridge between innate and adaptive immunity. They are found in the tissues, particularly in lymph nodes, skin and mucosal surfaces, where they sample the tissue environment. If a pathogen is detected, fragments of it are presented at the DC surface. Antigen presentation in this

way is necessary to activate adaptive immunity. In addition to causing cytokine secretion, signaling through the TLRs of DCs also causes them to express co-stimulatory molecules. This is important because it constitutes the secondary signal that is required to activate T cells of the adaptive immune system. In this way, DCs prevent an adaptive response from being mounted against a non-pathogenic antigen, such as a self-antigen or an environmental antigen. In the avian system, it is unclear whether macrophages and DCs are distinct populations, or which cell type activates the adaptive immune system.

Functions of dendritic cells

Dendritic cells perform three major functions: 1) they serve as sentinel cells and activate innate defenses when needed; 2) they process and present antigens, and therefore, initiate adaptive immune responses; and 3) they regulate adaptive immunity by determining whether an antigen will trigger an antibody- or a cell-mediated response. DCs are the only APCs that can activate those T cells that are naive to an antigen, and therefore, they are essential for initiating primary immune responses. When T cells detect presented antigens, they become activated. It is also worth noting that pathogens can evolve to evade immune detection, e.g. Marek's disease virus downregulates expression of the molecules that are used to present antigen, thereby impairing the process.

Activation of adaptive immunity in animals

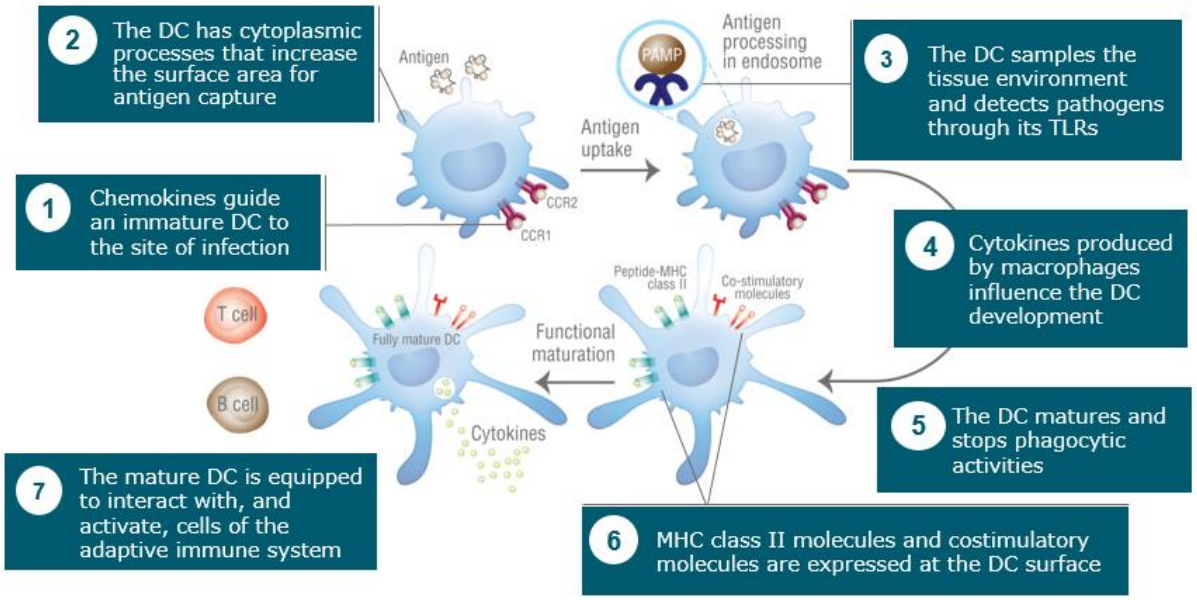
Through a combination of the major functions of DCs, the innate and adaptive arms of the immune system are linked. For instance, chemokines produced by macrophages in response to a pathogen guide immature DCs to the site of infection. The DCs sample the tissue environment and detect pathogens through their TLRs. On recognition of a pathogen, the DC matures and becomes able to present antigens and activate cells of the adaptive immune system, such as T cells (Figure 8). T cells can then go on to activate B cells, which secrete antibody that can bind to the pathogen.[31,32]

Adaptive immune cells offer a more targeted attack on the infecting pathogen and once the pathogen has been removed, the adaptive response ensures that the animal is protected from a repeat attack by the same pathogen.

Immune modulation by other types of cell

Mast cells and basophils also secrete products that modulate immune responses. Mast cells can be found at surfaces exposed to microbes, e.g. skin and mucous membranes. Their granules contain histamine, lipid mediators, cytokines and chemokines, and they express many receptors, including TLRs.[32] Mast cell products can direct immune cells to an infection site and modulate DC activation, antigen presentation and expression of costimulatory molecules, which influences adaptive responses.[33] Basophils are mainly found in the blood, and are relatively uncommon. Their granules contain vasoactive molecules, similar to those found in mast cells, and are probably involved in more chronic inflammatory states. Basophils drive an antibody-mediated adaptive response by production of interleukin (IL)-4, which directs Th2 differentiation.[32]

Figure 8. Dendritic cells are innate immune cells that link innate and adaptive immune responses[34,35]



DC, dendritic cell; MHC, major histocompatibility complex; TLR, toll-like receptor.

Summary

Summary of innate immunity

- Physical barriers protect animals from invasion by pathogens, however if they are overcome, the cells of the immune system fight the invading pathogen[36]
- Innate immunity acts rapidly, providing a broad response to a range of pathogens, while adaptive immunity takes longer to develop but provides a highly specific response to a particular type of pathogen[37]
- An adaptive immune response can only proceed when it has been activated by cells of the innate immune system; dendritic cells are the link between innate and adaptive immunity[36]
- Phagocytes can internalise and destroy pathogens with toxic products[37]
- Molecules that are found on microorganisms but not on vertebrate species are used to distinguish self-cells from pathogens[36]
- These molecules are known as PAMPs and can be detected by receptors called TLRs that are found on innate immune cells[36]
- When a PAMP binds a TLR, innate immune cells are activated and produce cytokines, which are proteins that can signal to other immune cells to attract them to the site of infection and become activated[5]
- When DCs detect a pathogen, they develop characteristics that enable them to activate T cells of the adaptive immune system, which in turn activate antibody-producing B cells[36]

(TLRs – Toll Like receptors, PAMPs – Pathogen Associated Molecular Pattern,DCs – Dendritic cells)

References

1. Tizard IR. Veterinary Immunology, 9th edn, 2013:3–5.
2. Murphy K. Janeway's Immunobiology, 8th edn, 2011:3,11,12.
3. Ricklin D & Lambris JD. Nature Biotechnol 2007;25:1265–75.
4. Murphy K. Janeway's Immunobiology, 8th edn, 2011:3,7,12,13,35,347–9,353–6.
5. Akira S, et al. Cell 2006;124:783–801.
6. Medzhitov R, et al. Nature 1997;388:394–7.
7. Image available from: http://jonlieffmd.com/blog/neurons-and-immune-cells-working-together-to-identify-self-and-other. Accessed April 2015.
8. Murphy K. Janeway's Immunobiology, 8th edn, 2011:5–8,11,12.
9. Kopp E & Medzhitov R. Current Opin Immunol 2003;15:396–401.
10. Akira S, et al. Phil Trans R Soc B 2011;366:2748–55.
11. St Paul et al. Vet Immunol Immunopathol 2013;152:191–9.
12. Hemmi H, et al. Nature 2000;408:740–5.
13. Griebel JP, et al. Vet Immunol Immunopathol 2005;108:11–6.
14. Murphy K. Janeway's Immunobiology, 8th edn, 2011:5.
15. DeFranco A, et al. Immunity. Sunderland, MA, US, New Science Press, 2007:34–7,76–7.
16. Li X, et al. Cytokine 2010;49:1–9.
17. Murphy K. Janeway's Immunobiology, 8th edn, 2011:9–101.
18. Tizard IR. Veterinary Immunology, 9th edn, 2013:217.
19. Tizard IR. Veterinary Immunology, 9th edn, 2013:61.
20. Murphy K. Janeway's Immunobiology, 8th edn, 2011:61–82.
21. Murphy K. Janeway's Immunobiology, 8th edn, 2011:12,810.
22. Tizard IR. Veterinary Immunology, 9th edn, 2013: 12,13,22–23,31,35–39,43–47.
23. DeFranco A, et al. Immunity, 1st edn, 2007:56,72–3.
24. Tizard IR. Veterinary Immunology, 9th edn, 2013:35–9.
25. DeFranco A, et al. Immunity. Sunderland, MA, US, New Science Press, 2007:56,72–3,82–3.
26. Murphy K. Janeway's Immunobiology, 8th edn, 2011:11,76–83,264–7.
27. Tizard IR. Veterinary Immunology, 9th edn, 2013:75–83,92,94,95.
28. DeFranco A, et al. Immunity. Sunderland, MA, US, New Science Press, 2007:82,83.
29. Murphy K. Janeway's Immunobiology, 8th edn, 2011:83,84.
30. Murphy K. Janeway's Immunobiology, 8th edn, 2011:342–9.
31. Murphy K. Janeway's Immunobiology, 8th edn, 2011:347–9.
32. Tizard IR. Veterinary Immunology, 9th edn, 2013:75–83,92–95,332–5.
33. Abraham SN and St John AL. Nat Rev Immunol 2010;10:440–52.
34. DeFranco A, et al., Immunity. Sunderland, MA, US, New Science Press, 2007:98–9.
35. Tizard IR. Veterinary Immunology, 9th edn, 2013:91,92,94,95.
36. Murphy K. Janeway's Immunobiology, 8th edn, 2011:11,12,43,44,77,347–9.
37. Tizard IR. Veterinary Immunology, 9th edn, 2013:4,6,16,17,35–46.