Physiology of immune competence

Andrew R Gennery

Abstract

When evaluating a child with recurrent infection or suspected immune dysfunction it is important to keep in mind the different components of a fully competent immune response. There are three main parts. A healthy and competent immune response requires an effective (i) barrier to infection (ii) innate immune response and (iii) adaptive immune response. An understanding of these discrete systems and how they interact allows clinicians to undertake investigation and management in a strategic manner, moving beyond a 'tick box' approach to immune dysfunction. This review will outline different elements of the immune system, with specific reference to defects that can lead to disease in humans.

Keywords adaptive immunity; host defence; immunodeficiency; innate immunity; microbiome

Introduction

The immune system has co-evolved with microbes over billions of years to provide efficient, self-limited host defence against the biotic and abiotic environment whilst preserving self-tolerance. It is composed of three elements; effective physical and mechanical barriers, non-specific innate immunity and specific, personalised adaptive immunity. The immune system is a complex interconnected network of proteins and cells, functional throughout the body, with a few specialised 'immune organs' including the bone marrow, thymus, spleen, lymph nodes and less discrete collections of lymphoid tissue – the mucosal- and bronchial-associated lymphoid tissue as well as Peyer's patches in the gut. The system is in part regulated by the microbiota which colonise each individual, and in that sense, the gut and liver, skin, and epithelial surfaces can also be considered as immune organs. Over our evolutionary history, different elements have developed as microbes have evolved, so that there is some overlap and redundancy. The three key components of human immune defence are (i) barriers, (ii) innate immune response and (iii) adaptive immune response. Their principal components are summarised in Table 1.

Barriers

Although rarely considered when evaluating patients with recurrent infection, mechanical barriers, in combination with associated chemical and microbial elements, are extremely effective at preventing microbial penetrance. Consideration of the extreme susceptibility of patients with severe burns, or epithelial defects found in cystic fibrosis, cilial dyskinesia or epidermolysis bullosa illustrate how effective intact and functioning physical barriers are at preventing infection. Fatty acids and enzymes found in secretions, as well as the pH of specific sites, such as the stomach also have an inhibitory effect on invading micro-organisms. Finally, the microbiota play an extremely important role, not only in inhibiting potential pathogens by competing for nutrients (demonstrated when antibiotic use selectively removes commensals allowing overgrowth of more pathogenic micro-organisms), but also, critically in modulating and shaping immune responses. It has only recently been appreciated how important these commensals are, now with a recognition, that diet can influence the diversity of gut microbiota and dominance of particular taxa that can induce a pro-inflammatory predisposition of the immune system, leading to diseases as diverse as Parkinson's disease, non-insulin dependent diabetes mellitus and intravascular inflammation predisposing to arteriopathy, cardiovascular disease and obesity. For instance, complex plant polysaccharides and ω-3 fatty acids play a role in promoting growth of microbes that diminish recruitment of immune cells to the gastrointestinal epithelium, increase apoptosis and reduce pro-inflammatory cytokine production. Our understanding of the importance of the microbiota, not only of the gastro-intestinal tract, but also respiratory, genito-urinary and dermal surfaces is only just beginning to uncover its role in disease, and how modulating the microbial families can influence disease courses.

The components of the human immune system

Barriers	Innate	Adaptive
Skin, hair, nails Cilia Mucus membranes Mucus, tears Digestive enzymes Stomach acid Commensal bacteria	Cellular Neutrophils Eosinophils Basophils Macrophages Natural Kill Cells Humoral Complement Mannose binding lectin	Cellular T lymphocytes B lymphocytes Humoral Antibodies Cytokines

Table 1

Innate immunity

The innate immune system is the oldest limb of our immune system, and consists of cellular and humoral elements. Initiation of the innate response is rapid, occurring within 0–4 hours, an important characteristic of the response given that the internal milieu of humans, with a warm, oxygen and nutrient rich environment is an ideal culture medium for many microbes, which can double every 20 minutes. The response is not antigen-specific, with a similar magnitude of response at repeated antigen encounters. Whilst generally said to have no 'memory' for specific antigens, the innate response can be thought to represent

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a common 'race memory', which our species has acquired over our evolutionary history, and which is encoded in the germline. This memory is shared between all individuals, and is not possible to modify.

Cellular elements of innate immunity

The cells of the innate immune response consist of phagocytes and Natural Killer lymphoid cells and are derived from haematopoietic stem cells in the bone marrow. There are numerous types of phagocytes, which share a common ability to bind to pathogens via non-antigen-specific receptors — the **pattern recognition receptors** that recognise repeating patterns of highly conserved molecular structure found on microbes, but not as part of 'self' — the **pathogen-associated molecular patterns**. These receptors are encoded in germline DNA and are the same for each individual. They are not organism-specific and include bacterial wall peptidoglycan or lipopolysaccharide, and fungal glycoproteins (mannans). After binding to these molecules, the effector cell is activated immediately, accounting for the rapid response of the innate system. Once bound to a receptor, the pathogen is internalized or phagocytosed as it is surrounded by phagocyte membrane and internalised in the membrane-bounded vesicle (known as a phagosome or endocyte vacuole). The phagosome becomes acidified due to production of respiratory by-products produced by the internalized micro-organism, and generation of reactive oxygen species by the cell released during the phagocyte respiratory burst and mediated by enzymes such as nicotinamide adenine dinucleotide phosphate (NADPH) oxidase enzyme complex, responsible for producing reactive oxygen species (ROS). This process destroys many phagocytosed micro-organisms.

Phagocytes (Figure 1) include:

- neutrophils, the most abundant leukocytes, which express receptors for immunoglobulin and complement and are involved in the acute inflammatory response
- eosinophils, which carry receptors for immunoglobulin E (IgE), and are involved in the destruction of IgE-coated parasites such as helminths, and also contribute to the response to allergens
- basophils, which are the circulating counterpart of tissue mast cells and express high affinity receptors for IgE. They secrete the chemicals responsible for immediate hypersensitivity following antigen-induced aggregation of these receptors
- Natural Killer cells, a large granular lymphoid cell of the innate system which does not possess an antigen receptor, but does possess FcγRIII receptors which binds to IgG1 and IgG3, and is cytotoxic to tumour cells and virally-infected cells. They produce cytokines, particularly gamma interferon (IFNγ).

Macrophages are tissue monocytes, and are an important mediator between innate and adaptive responses, with dendritic cells. Depending on the anatomical site, they may go by different names, including Kupffer cells in the liver, Langerhans cells in the skin, microglia in the central nervous system, and alveolar macrophages in the lung. They act as 'sentinels' — particularly under skin, gut and respiratory mucosa, processing dead cellular debris from the natural cell death, which is constantly occurring in a healthy individual. In this state, they are quiescent, and do not cause inflammation. Dendritic cells are bone-marrow derived leukocytes which are responsible for the initiation of adaptive immune responses — they are the most potent type of antigen-presenting cells. Dendritic cells are specialised to capture and process antigens, converting proteins to peptides that are presented on major histocompatibility complex (MHC) molecules, which are subsequently recognised by T-lymphocytes. When barriers are penetrated, IFNγ is released by Natural Killer cells and tumour necrosis factor alpha (TNFα) is secreted by antigen presenting cells, which induce up-regulation of major

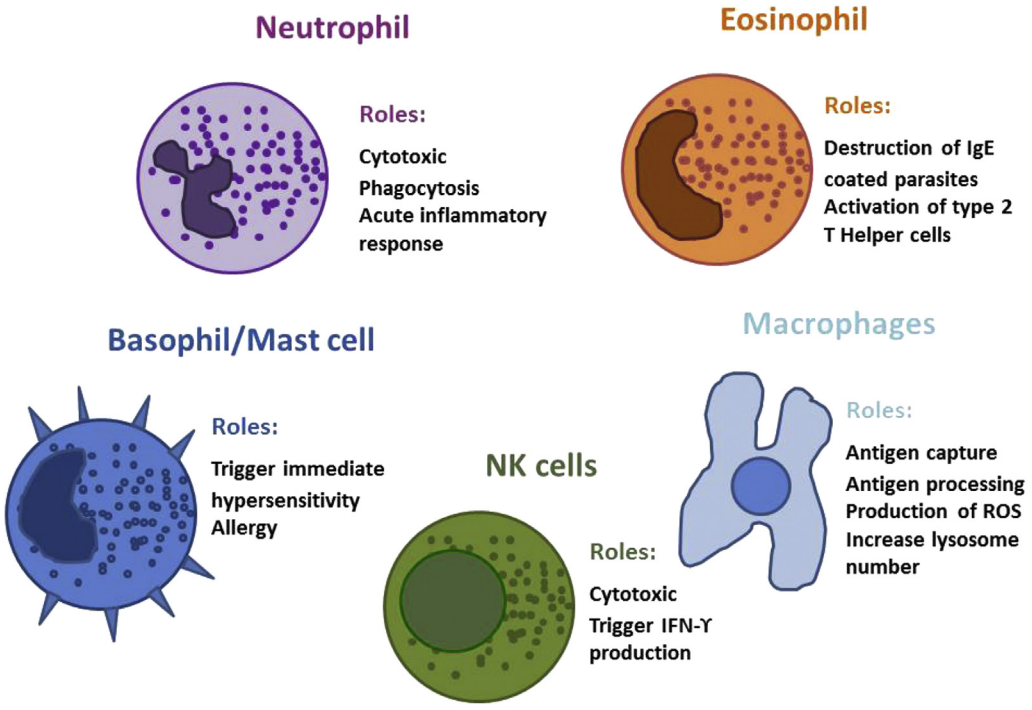

Figure 1 Phagocytes and their functions.

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