Section B and C

Volume-07

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4. CELL COMMUNICATION AND CELL SIGNALING

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E. INNATE AND ADAPTIVE IMMUNE SYSTEM

1. INTRODUCTION:

All living things – animals, plants and even bacteria – can act as hosts for infectious organisms and thus have evolved mechanisms to defend themselves against infection. Infection can be by other living things, non-living things (viruses) and possibly even molecules (prions). Since it is so crucial to our own survival, much of our understanding of immunity has come from studies in humans – particularly in relation to the causes and prevention of disease – but deep insights have also come from experimental studies in animals such as mice. For these reasons, in this book we concentrate on the immune systems of humans and mice. These, along with other more recently evolved organisms (e.g. birds and amphibians), have the most complex and sophisticated immune systems, but the origins of these can in many instances be traced back to the most distant and ancient species in evolutionary history.

We need immune responses to defend ourselves against infection. Many different kinds of organism have the potential to infect us and, if they do so, can cause us harm in many different ways. To deal with all these potential threats we, as hosts for infectious agents, need a variety of different kinds of host defence mechanisms. Indeed this applies for any living organism.

1. Host Defence

All organisms possess mechanisms to defend themselves against infection, and immunity is a specialized form of host defence. In mammals, defence mechanisms can be passive or active. Passive defence comes in the form of natural barriers that hinder infection. Examples are skin, which prevents access of microbes to the underlying tissue, and gastric acid in the stomach which, not surprisingly, can kill many microbes that might be ingested with food. Their existence is quite independent of the presence of infection. Active defence is brought about by immune responses that involve a diversity of different effector mechanisms that are induced by the presence of infection and which may eliminate the microbe. Thus, all forms of active immunity depend on specific recognition of molecules present in the infecting agent. This is turn leads to a response, involving the interaction of cells and molecules to produce different effector mechanisms that can often eliminate the infection.

Immunity is itself divided into two different forms – innate and adaptive. Innate responses occur rapidly and can generate effector mechanisms that are effective within minutes or hours of infection. In contrast, adaptive immunity takes much longer to become effective,

usually over a few days. In immunity to most forms of infection, however, both innate and adaptive immunity are essential. A major advantage of adaptive immune responses, not seen with innate immunity, is that they generate memory – a second infection with the same microbe elicits a stronger, faster and usually more effective response.

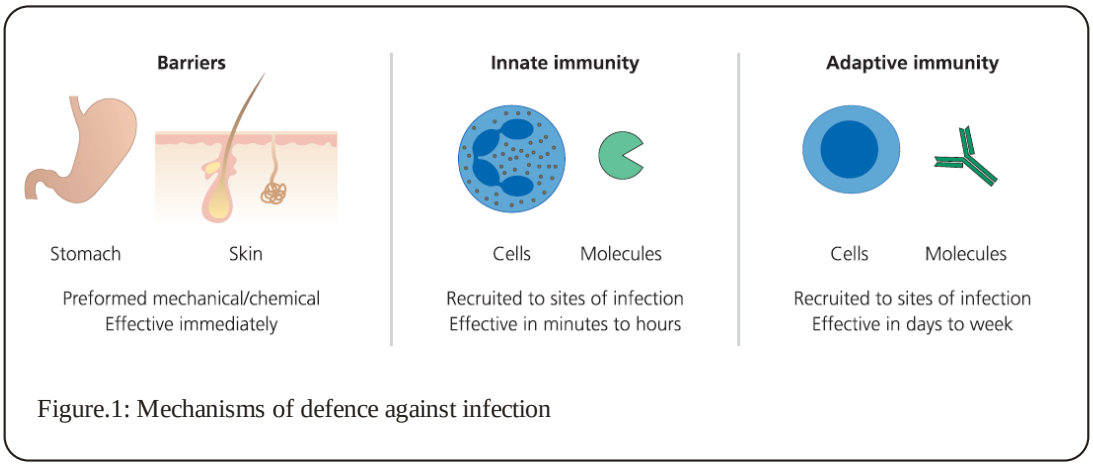

Figure.1: Mechanisms of defence against infection

2. Immune Recognition:

Different types of cells and molecules are involved in the initiation of innate and adaptive immune responses although, as mentioned above, their interaction is essential in defence against most infectious agents. So what do the innate and adaptive arms of immunity do in general terms? Broadly speaking we can view some components of the innate immune system as being involved in the detection of harmful things that represent danger to the organism, such as general classes of microbes that may have infected the host.

Other components then endeavour to eliminate the microbe. In contrast, the adaptive immune system can discriminate very precisely between individual microbes, even of the same type, but can generally only make a response if it has been informed by the innate system that what is being recognized is .dangerous.. If so, adaptive responses may then help to eliminate the microbe, if it has not already been eradicated during the earlier innate response. Recognition of infectious agents is essential for any form of immunity and thus for host defence against them. Generally speaking, the types of receptors used for recognition differ in innate and adaptive responses.

a) Recognition in Innate Immunity: Pattern Recognition Receptors

The key components of the innate immune system include cells such as phagocytes and soluble molecules such as complement. These work together to sense the presence of infection. The recognition of potentially dangerous microbes usually leads to the generation of inflammation. One way of viewing this is that the innate immune systems of multi-cellular

organisms can generate alarm signals in response to danger, and that some of these signals cause inflammation. Alarm is not a conventionally used term, but is one that we find helpful and therefore will use it from time to time in this book. Inflammation enables effector cells and molecules to be targeted to the site of infection. As noted above, other signals generated during innate responses can also determine whether, and in what way, the lymphocytes of adaptive immunity will respond.

The recognition of infectious agents in innate immunity is mediated by germline-encoded receptors called pattern recognition receptors (PRRs). These receptors generally recognize conserved features of infectious agents that are often shared by different classes of microbes, these microbial features are called pathogen-associated molecular patterns (PAMPs). PAMPs directly or indirectly stimulate innate immune responses by acting as agonists for PRRs. An agonist is anything that stimulates a response through a receptor, as opposed to an antagonist that inhibits it. PAMPs may bind directly the PRRs, therefore acting directly as ligands for these receptors, but some PAMPs can trigger responses by binding to a different molecule that then associates with a PRR, so it is useful to use the general term agonist. This also allows us to discriminate clearly between components of microbes that trigger innate responses, and molecular structures which are recognized in adaptive immunity that are termed antigens. The cells responsible for initiating activation of the innate immune system are widely distributed in tissues and organs, and they possess many copies of different types of PRR that trigger rapid responses. This allows very rapid activation and deployment of the effector mechanisms of innate immunity. In many cases the innate system can eliminate the infectious microbe, often without any symptoms occurring (i.e. sub-clinically), and if there has been damage to the tissues at the site of infection the innate system will initiate repair and healing. Importantly, activation of the innate system is also essential for the triggering of adaptive immune responses

b) Recognition in Adaptive Immunity: Antigen Receptors

The key components of the adaptive immune system are the lymphocytes. It is convenient at this stage to divide these into two main groups (other types do exist). One group is the T lymphocytes (T cells) which have evolved to interact with other cells. The other is the B lymphocytes (B cells) which are the precursors of cells that can make soluble antibodies. The recognition of molecules from infectious agents by lymphocytes is mediated by their specialized antigen receptors, which are not present on cells of innate immunity. An antigen can be defined as a molecular structure against which a specific adaptive immune response can be made. In contrast to PRR agonists in innate immunity (above), the antigens which stimulate lymphocyte responses are generally unique to particular infectious agents no matter how closely they are

related. Collectively, lymphocytes express a vast range or repertoire of antigen receptors of different specificities, but each lymphocyte expresses multiple copies of a receptor of only a single given specificity. The term specificity relates to the particular antigen(s) that each lymphocyte is able to recognize. These receptors are generated by rearrangement of germline DNA, a process that is not known to occur for any other type of molecule. Their specificity is generated largely at random and in advance of any infection. Lymphocyte recognition of antigen is thus anticipatory. Lymphocyte antigen receptors are highly discriminatory and distinguish between even very small differences in antigens, such as an amino acid substitution in a peptide or a specific side chain in an organic molecule.

c. Types of Recognition in Innate and Adaptive Immunity

Earlier, we suggested that some components of innate immunity can be viewed as recognizing danger, and that in general they are able to discriminate between harmful and harmless stimuli. Danger can be represented by the presence of an infectious agent or by signs of cell damage or stress that may or may not be associated with infection. In contrast, the antigen receptors of lymphocytes enable them to discriminate very precisely between what is self (any normal component of the host) and non-self (such as a component of a microbe), but not between harmless and harmful. Therefore, it is primarily the signals generated by the innate system that inform lymphocytes as to whether the antigens that they are recognizing originate from harmful or harmless agents, and hence determine whether or not these lymphocytes become activated and also precisely how they need to be activated in the context of the specific danger that is posed. If they are instructed that there is no danger (or not instructed that there is danger), then lymphocytes become unresponsive, or tolerant to what they are recognizing.

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