Immune System: General Characteristics

Organisms are connected in a complex web of relationships. Although many of these are benign, not all are, and everything alive devotes significant resources to identifying and neutralizing threats from other species. From bacteria through to primates, the presence of some kind of effective immune system has gone with evolutionary success.

The problems that the mammalian immune system solves are not restricted to higher animals; they are faced by all forms of life and are ignored by none. The pressure that natural selection exerts is inexhaustible and unending. Emerging infectious diseases have as much potential to shape future human history as the epidemics and pandemics of the past. Managing this threat depends on understanding how to maximize the potential of our sophisticated immune system in the service of human health.

It is a fundamental property of immunity that no part of our body is cut off from its surveillance. For this reason, although the immune system may seem a less substantial thing than an organ such as the heart or the liver, in the aggregate, immunity consumes enormous resources, producing the large number of cells that it depends on for successful functioning. After early childhood, most immune cells are produced from the bone marrow. Some of these then undergo very significant secondary education before they are released to patrol the body. Many important immune cell types have been identified. In a routine blood test, five different kinds of white blood cell will be counted. An immunologist or a haematologist may subdivide these populations further, on the basis of the proteins that are expressed in their cell membranes. Among these proteins are receptors by which cells interact with each other and the environment. Receptors bind ligands which may be receptors on other cells, or soluble molecules such as cytokines. Cells express hundreds of different types of receptor on their surface. Many carry out fundamental functions, such as transporting glucose into the cell. The receptors associated with the immune system are generally concerned with interrogating the environment for evidence of danger, infection or abnormal cell death. In the course of an immune response, cells follow a programme, such that the overall outcome maximizes the likelihood of surviving and eliminating infection or cancer.

Receptors are also present inside the cell where they play an important role, acting to detect sign of infection. Organisms such as viruses can spend most of their life hidden in the complicated cytoplasm of the cell, making them difficult to recognize from the outside. Receptors within the cytoplasm can bind to virus-derived signature molecules, such as different types of nucleic acid and signal that infection is present. Cells use a sophisticated system for sampling the proteins they are making, to check that none have come from viruses. If cells detect such telltale signs they respond, by producing cytokines that serve as alarm signals for surrounding tissues, and by committing rapid and effective suicide that leaves a cell remnant that can initiate adaptive immunity directed at the inciting infection.

Tackling infections is the job of different types of white blood cell. Early in an immune response, the most important of these are the innate immune system cells neutrophils and macrophages, which are the first at the scene of an environmental breach, such as an insect bite. Both of these cell types are effective killers in their own right. They secrete highly destructive

substances including enzymes that digest proteins and reactive chemicals such as bleach that kill. Then they engulf and digest what they have damaged, a process called phagocytosis. Infections that are not destroyed by this attack attract the attention of lymphocytes. These cells embody the functions of adaptation and memory, allowing the immune system to make increasingly specific responses and to remember individual types of infection, so that reinfection is met with a faster and more effective counterattack.

All of these different responses rely on the selective expression of specific families of genes. Studies of the immune system have been at the forefront of characterizing how different gene programmes function. Immune cells read the environment through their receptors and then modify how they use the genes encoded by their DNA. Some groups of genes are switched on, and others are switched off. This gives the different cell types a great deal of flexibility in how they handle an infection. Sometimes these gene programmes change the cytokines that cells secrete, sometimes they change the pattern of receptors on the surface and sometimes they change how resistant the cell is to infection. Information in the environment can label a specific location, keeping immune cells from moving away. Other signals affect the whole body, such as the cytokines that stimulate changes in the regulation of body temperature that lead to fever. The adaptations that we make in response to infection are measured over many time scales. They may occur rapidly in minutes and resolve just as fast; they may continue for days until a viral infection is cleared or they may be long-lasting and change the local anatomy of a tissue such as the autoimmune disease rheumatoid arthritis. The immune system is, then, a highly connected web of many different types of response deployed to maintain the status quo of a pathogen-free internal environment.

An effective immune system must be able to interpret changes in the world around it and respond appropriately. To do this, it has to solve a number of specific problems.

Discrimination

Immune systems have an uneasy relationship with the environment. Most of the time an encounter with something new is harmless, but the small fraction of times that it is not can be very dangerous indeed. An effective immune system must be able to discriminate such differences, distinguishing self from non-self and distinguishing harmless non-self from dangerous non-self. For much of the 20th Century, research in immunology was focused on understanding how it achieved the former. It was spurred by an important early observation: that it was possible for animals to develop specific immune reactions against chemicals such as dyes, which had never existed in Nature. The ability to learn how to recognize these previously unknown structures implied that the immune system had solved the problem of how to classify and recall the shapes of individual molecules. Unravelling the biological machinery that achieves this was a signature achievement of 20th Century immunology.

This remarkable flexibility underlines the fact that the immune system interrogates the fundamental building blocks of the environment. A process of recognition at a near molecular scale allows the immune system to exploit the fact that all organisms are defined by proteins encoded in their genes. A measles virus is made of different proteins from those of a rabies virus. An Escherichia coli bacterium has a different structure from that of a spirochaete. By classifying the environment in terms of the proteins it contains, and by continuously sampling these proteins, the immune system executes a very active form of monitoring that it links to a

stringent verification process and which must incorporate an ability to learn. As part of a defense against a potentially dangerous environment, each individual develops their own unique immune system, which acknowledges only itself. Everything that is not recognized might be a threat.

Flexibility

The immune system's ability to adapt flexibly to strange environmental changes is critical in fighting infections and cancer. Because our bodies have a remarkable capacity for renewal, and almost every cell is a factory working day and night to turn over worn out molecules, breaking them down into building blocks that are reused to make replacements, infection or cancer can arise at any time. Every time a cell divides, there is a small chance that it may develop a random unpredictable mutation that will transform it into a cancer. Infections reproduce much more rapidly than their hosts and can change their appearance to allow them to evade recognition. An effective immune system must cope with this unpredictability.

We can picture this as an ongoing evolution of the environment and it presents a special challenge for an immune system. In contrast with most organs, such as the heart, which does the same job throughout life, the immune system needs to adapt to an environment that is always changing. This problem is solved by investing in strategies that exploit the power of random change itself. Using randomness in this way creates waste, but preserves responsiveness. Even identical twins, which share the same genes, have immune systems that become increasingly different from each other from birth to old age, as each twin independently makes hundreds of thousands of unique random responses to the environment.

Managing infection

For a microbial infection to develop, the pathogen must get close enough to interact with individual cells. The skin and mucous membranes make this close approach difficult. Physical barriers provide innate protection, such as the tough overlapping cells of the skin and chemical barriers, and enzymes, such as lysozyme in snot and tears and the acid in the stomach, also kill many bacteria. These outward-facing surfaces actually encourage the presence of non-pathogenic microbes. By welcoming and supporting a co-operating microbial population, little opportunity is left for more dangerous relatives to move in. The healthy immune system lives happily with this symbiotic microbial farm, but still reacts when there is a dangerous infection. As our understanding of the ecology of this ‘microbiome’ grows, it may offer new therapies that can support the exclusion of disease causing organisms.

When pathogens do penetrate these defences and seek to live within our bodies and within our cells, they pose many threats, from quiet coexistence to wholesale cell destruction and death. There is wide diversity in pathogens’ methods of attachment and entry. For every individual pathogen, this process is tailored to species, to specific cell types and to defined cell-surface receptors. Each infection uses a different door into the cell. Blocking off these routes of entry can stop an infection before it starts. By producing antibodies, the immune system can neutralize an infection before the key to the cell turns in that particular doorway. But this must be carried out one key at a time.

A pathogen that has penetrated the defences of the skin and mucous membranes and

established itself within or between cells, or a cell that has turned into a cancer, can only be eliminated by killing. This is a dangerous business, and when the immune system is battling with an infection, it may put the life of the host at risk. Sometimes when it is not infection, but an adverse reaction to a drug or a treatment for cancer which activates the immune system, this leads to critical illness. There is a delicate balance between what is successful and what is sustainable when invoking a full-blown immune reaction.

Moreover, some infections cannot be killed off reliably by the immune system. Viruses that evade immunity, by hiding within cells, lead to repeated bouts of illness as limited as cold sores or as destructive as AIDS. Cancers that escape from immune control can continue to grow, may metastasize and then kill in different ways.

In meeting all of these kinds of assault, there is a middle path that an immune response must keep to, between too much destruction and not enough. In this zone, it is quite ruthless in sacrificing itself to terminate an infection. When common cold viruses have hijacked cells in the throat to replicate, these virus factories are not rehabilitated, but destroyed by killer cells. Where a bacterium has penetrated the skin and established a viable colony, suicidal white blood cells fill the area with bleach that they make themselves, killing indiscriminately and leaving behind a wasteland of debris that needs to be engulfed, digested and processed by the immune system.

Memory

One of the most significant features of the immune response is its ability to retain a memory of previous infections. This both protects individuals from reinfection and limits the spread of infection in a community. Immune memory can be very long-lasting; when adults were studied, their memory for the measles infection was decaying so slowly, it would have taken over 3000 years to decrease by half. This goes well beyond life-long protection. These robust durable changes are the reason that, when we vaccinate, the protection this produces delivers long-term benefits.

Within an individual, immune memory must be distributed throughout the body. Circulating antibodies travel in the blood, reaching everywhere the circulation does; memory also develops outside the bloodstream within tissues. Killer cells can remain on guard where the immune defences broke down in the past, alert but not activated, ready to attack rapidly if reinfection occurs.

Finally, some infections have such a profound impact on a species that the imprint of individual pathogens can be perceived in the tree of evolution. If an infection is lethal, only individuals who have genes that encode effective resistance will survive to produce the next generation. Modern methods of analysing inheritance have demonstrated how the co-evolution of host and infection has shaped the make-up of the immune system and the receptors it uses for recognizing and fighting pathogens.

All immune systems address and solve these challenges. How mammals achieve this complex task is the story of an integrated system of biological processes, often using strategies that surprised their discoverers, whose elegance and power continue to provide new insights for students of immunology young and old.