Lymphocyte Homing in the Immune System

Overview

There are 3 interconnected layers of defense against attack by pathogens:

- Physical barriers: external epithelial layers, mucus and other secretions containing anti-microbial molecules, internal anatomical barriers (fasciae, pleura, peritoneum etc.). Mode of action: *exclusion and confinement.*

- Innate immune system: tissue-resident "guardians" (mast cells, macrophages, Langerhans cells and other DC); blood-borne "rapid response" cells (neutrophils, monocytes and their offspring, eosinophils, NK cells); soluble mediators (natural antibodies, complement, acute phase proteins etc.). Mode of action: *pre-programmed, hard-wired, instant responses to physical injury and/or pathogen-associated molecular patterns (PAMPs); no memory* (more details in the Ezekowitz lecture).

- Adaptive immune system: B and T cells. Mode of action: *pathogen-specific humoral and cellular responses; long-lived memory.*

An every-day example: the epidermal barrier has been breached, bacteria have entered the subdermal tissue.

- The alarm bells start to ring because:

  Physical injury to tissue (induced by toxic bacterial metabolites or physical trauma) is sensed in form of distress signals (interleukins, interferons, TNF, HSPs, PAF, leukotrienes etc.) released from parenchymal cells, compromised vascular integrity induces platelet activation, coagulation, extravasation of plasma proteins (Ig, complement), which recognize PAMPs.

  Tissue macrophages and mast cells express multiple receptors for PAMPs (e.g. LPS receptor, mannose binding protein, formyl-peptide receptor), for PAMP-induced humoral factors (activated complement, immobilized antibodies), and for tissue distress signals. Their response: phagocytosis/killing of bacteria and amplification of distress signals by release of secretagogues (e.g. histamin, thrombin, serotonin etc.), cytokines (e.g. TNFα, IL-1, IL-6) and inflammatory chemokines (e.g. IL-8, MCP-1 etc.)

- The rapid response force is being deployed:

  The microvasculature responds to inflammatory stimuli by: vasodilation causing hyperemia (*redness* and *heat*); increased permeability (edema, *swelling*) allowing extravasation of macromolecules; expression of adhesion molecules and chemoattractants for myeloid cells.

  Neutrophils are now recruited to the site of injury (monocytes and macrophages arrive somewhat later). Intravascular adhesion requires sequential action of (1) selectins and their sugar ligands (which

mediate *rolling*) and (2) a chemotactic stimulus that triggers (3) activation of ß2 integrins (*firm arrest*). The adherent cells migrate through the vascular wall (*diapedesis*) and remove bacteria by phagocytosis, production of free radicals (oxidative burst), release of anti-bacterial proteins (e.g. proteases, defensins) and more cytokines and chemokines. After bacteria have been cleared, macrophages restore the tissue by phagocytosis of cellular debris, release of growth factors and stimulation of fibroblasts to form a scar.

How the incident is remembered.

- Tissue-resident dendritic cells translate and confer the "pathogen!" message to lymphocytes:

A meshwork of immature dendritic cells (in the skin they are called Langerhans cells) resides in a subepithelial layer (scattered DCs are also found deep within soft tissues and solid organs). They have potent endocytic and phagocytic activity. Many factors associated with tissue inflammation (TNF, LPS, dsRNA etc.) induces their maturation and migration into local lymph vessels and from there to draining LNs. Thus, they carry and present bacterial Ag from the site of inflammation to a large number of lymphocytes. Some pathogens and or pathogen-derived antigenic material may also enter the blood stream. Circulating Ag is taken up by phagocytic cells (the so-called mononuclear phagocytic system (MPS), previously known as reticulo-endothelial system (RES)) that live within microvessels in the liver, bone marrow and the spleen. The spleen is the major site of immunization to blood-borne Ag.

- Stimulation of Ag-specific T and B cells induces proliferation and differentiation.

Short term effects are production of effector T cells (Th1, Th2, CTL) and IgM producing B cells. While most of these die as soon as the infection is cleared, some Ag-experienced lymphocytes remain. These memory cells mediate enhanced recall responses upon re-encounter of the pathogen. Plasma cells generate high affinity circulating antibodies that neutralize reactive pathogens and/or mark them for rapid phagocytosis.

The adaptive immune system

Mode of action: *pathogen-specific humoral and cellular responses; long-lived memory*. Adaptive immunity must deal with pathogens that escape innate immune mechanisms, e.g. because they hide inside the body's own cells (e.g. virusses, some bacteria) or because they are the body's own cells (e.g. malignant cells or autoreactive lymphocytes; both have no PAMPs!) or because they have developed resistance to innate effector mechanisms (e.g. mycobacteria or parasites). These threats to the body's integrity are recognized because they generate non-self molecular patterns, i.e. **antigens**.

Lymphocytes recognize Ag by virtue of their unique Ag receptor, which recognize structural features of foreign peptides or lipids presented in the context of MHC molecules or CD1, respectively.

Lymphocyte homing

A few simple rules (which have exceptions):
   - every lymphocyte has exactly one Ag receptor, which recognizes a unique "cognate" non-self Ag;

- naïve lymphocytes are stimulated by Ag only when it is encountered on the surface of professional APC together with appropriate costimulation;
- a diverse repertoire of Ag receptors is necessary to ensure that any conceivable pathogen can be recognized as such.

A strategic problem: The T cell compartment in a normal adult human contains up to 10^8 distinct clones each expressing a different αß TCR. Assuming that there are ~10^{12} T cells in a human, any given TCR is represented, on average, on a total of ~10,000 naïve T cells.

Secondary lymphoid tissues – graduate school for lymphocytes
- are organized to optimize the probability that a rare Ag-specific T cell encounters is cognate Ag on a professional APC;
- collect Ag and/or APC from the periphery and naïve B and T cells from the blood (recirculation), thus providing an interface between the innate and adaptive immune system;
- may confer tissue specificity to effector/memory cells