The endosome effect

Guiducci et al. report on page 1999 that plasmacytoid dendritic cells (PDCs) mount either innate or adaptive immune responses depending on the subcellular localization of foreign DNA.

PDCs are very rare in the body (making up less than 1% of the cells in the blood) but are important for antiviral immune responses. Activation of the endosomal receptor TLR9 by viral DNA can induce PDCs either to mount an innate response (marked by their ability to produce IFN-α) or to mature into antigen-presenting adaptive immune cells. How these two fates are determined was unclear.

The two fates can also be induced using three different classes of synthetic oligonucleotides called CpG immunostimulatory sequences. CpG-A normally induces IFN-α production, CpG-B induces maturation, and CpG-C can induce both. Now, Guiducci et al. show that the location of the oligonucleotides appears to determine PDC response: an early endosome location leads to an innate response, and a late endosome location leads to an adaptive response.

Oligonucleotide location could be manipulated based on oligonucleotide structure. The group found that multimerizing CpG-B switched its location from late to early endosomes and switched its effect from maturation to the induction of IFN-α production. The opposite transformation was possible with the normally multimeric CpG-A: reducing it to a monomer shifted it from early to late endosomes and altered the effect from IFN-α production to maturation.

CpG-C was found in both early and late endosomes, as might be expected based on its dual effect on PDCs. By preventing its interaction with TLR9 in early endosomes, the team found that CpG-C could no longer induce IFN-α production, but its ability to induce maturation remained intact.

Multiple questions remain. It is unclear why the spatial structure of the oligonucleotides would determine location or why location would determine the type of immune response. The larger mystery is why PDCs are using such a mechanism to regulate the nature of their immune response to viruses.

What we do know is that many viruses locate to early and/or late endosomes. The authors suggest that PDCs have adapted to this behavior of viruses and are able to mount the appropriate immune response for the stage of infection or the type of virus.

Bound for the brain

In a fast moving river, your chances of making it safely to the river bank are small. Similarly, a report by Mairey and colleagues, on page 1939, reveals that invading Neisseria meningitidis bacteria must rely on pauses in blood flow in order to attach to the edge of blood vessels.

Colonization of the nose and throat by N. meningitidis bacteria is not uncommon in the general population. If these bacteria gain access to the bloodstream, however, they can cause septicaemia and may even cross the blood–brain barrier to cause meningitis.

In brain samples from a meningococcal sepsis victim, Mairey et al. found that N. meningitidis were not distributed evenly throughout the blood vessels but were instead specifically restricted to capillaries. Since blood flow in capillaries of the brain has been reported to be very heterogeneous, their finding suggested that flow rate, or shear stress, might influence bacterial adhesion. Mairey and colleagues examined blood flow in the brain of live rats and found, to their amazement, that in some capillaries blood flow transiently slowed and sometimes even stopped.

In vitro, N. meningitidis bound readily to human endothelial cells under low-flow conditions but much less readily during faster flow. Once bound, the bacteria remained steadfastly attached even when the flow speed was subsequently increased. This slow-to-fast transition in flow rate essentially mimicked the changes in blood flow observed in the live rat brain, and the authors suggest that transient slowing of blood in the human brain provides N. meningitidis with the opportunity to bind to and subsequently breach the blood–brain barrier.

“It is not clear whether this [change in flow speed] happens more or less frequently in brain compared to other organs” says Guillaume Dumenil, who led the research. Indeed the team found N. meningitidis in capillaries of other organs. In the brain, however, there is evidence that astrocytes can cause the endothelial cells of arterioles to contract, thus reducing vessel diameter and potentially causing a temporary reduction in blood flow.
Is war necessary (for transplant success)?

If immune cells are an army, then a graft transplant is a foreign invasion. New work by Yu et al. on page 1851 shows that antigen-presenting cells (APCs) from the graft are rapidly killed by the host’s first line of defense: natural killer (NK) cells. But far from hindering the chance of graft survival, this battle actually improves it.

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Don't overreact

Response to microbial infection must be perfectly balanced to kill off the bugs but not the surrounding host tissue. Wirtz et al. (page 1875) report that in sepsis this balance fails. By attempting to prevent an overzealous innate immune response, the cytokine IL-27 prevents efficient bacterial clearance.

IL-27 is strongly induced by microbial stimuli in vitro, but its response to microbes in vivo was unclear. In a mouse model of septic peritonitis, microbial invasion from the gut triggered IL-27 production. IL-27 was produced earlier than cytokines of the adaptive immune response, IL-12 and IL-23, indicating that IL-27 induction was, in this case, part of the innate response.

In earlier studies, IL-27 was shown to promote T cell proliferation and thus positively regulate adaptive immunity. In the present study, however, IL-27 displayed a negative effect on the innate response: mice lacking functional IL-27 cleared bacteria more efficiently and were more likely to survive than their wild-type counterparts. The authors attribute this increased survival to a corresponding increase in the number and the oxidative burst activity of granulocytes found in the abdomen.

How IL-27 suppresses myeloid cell activation remains to be determined. Furthermore, “the normal physiological role [of IL-27] is still unclear,” says Wirtz. Its role in innate immunity, at least, is probably to limit inflammation and thus protect body tissues from damage. In the case of sepsis, however, this control goes too far. JEM

Why lymph nodes grow

At the initiation of an immune response, lymph nodes can double in size in a day and can be ten times their original size in five to seven days. Webster and colleagues report on page 1903 that dendritic cells, quite distinct from their function in antigen presentation, stimulate endothelial cell proliferation and vascular growth in the growing lymph node.

Peripheral challenge (such as immunization) induces dendritic cells to mature and migrate to the lymph nodes. But what is their role once there? Dendritic cells are well known for their role in B and T cell lymphocyte stimulation but, surprisingly, Lu’s team found that without lymphocytes (in Rag−/− mice) dendritic cells could activate lymph node growth and endothelial cell proliferation almost as effectively.

Vascular endothelial growth factor (VEGF) has been implicated in lymph node growth, and the team found that dendritic cells could increase VEGF levels in the lymph node, again, without the need for lymphocytes. Increased VEGF and increased endothelial cell proliferation required dendritic cell–mediated recruitment of cells from the circulation. Either these recruited cells or other lymph node cells (but not the dendritic cells) are then thought to produce the VEGF. Determining how VEGF levels are up-regulated is the subject of ongoing study.

Enlargement of the lymph nodes is a normal step in combating infection, but it also occurs during autoimmune responses. One possibility for combating lymph node growth during autoimmunity is antiangiogenic drugs, which were developed to combat tumors. JEM

Long–term survival of a transplant is improved in the presence of NK cells.

Using mice that lacked a full-blown rejection response (because they lacked lymphocytes), the team were able to follow the fate of donor APCs for longer than would normally be possible. They found that in the absence of NK cells, donor APCs could roam free in the host, as confirmed by their presence in spleen, liver, and lung. In the presence of NK cells, however, injected or graft-derived APCs were completely eliminated from the host.

The team reasoned that immediate destruction of the APCs by NK cells was preventing a more vigorous anti-APC response by host lymphocytes. To confirm this, they restored the T lymphocyte population of the mice and showed that, in the absence of NK cells, APCs activated robust and persistent T cell proliferation and IFN-γ production—marks of a ferocious immune response. But in the presence of NK cells this T cell activation was, as predicted, markedly reduced.

The daily immunosuppressants that transplant patients must take “are designed to suppress T cells,” says lead researcher Xian Li, “but we don’t know if they are also suppressing NK cells.” Drugs that specifically suppress T cells but boost host NK cells might therefore improve the outcome for transplant patients. JEM