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*Friedrich C. Luft*

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# Curbing the appetites of the big eaters

Friedrich C. Luft<sup>1</sup>

<sup>1</sup> Experimental and Clinical Research Center, Max-Delbrück Center for Molecular Medicine, Robert-Rössle-Str. 10, 13125 Berlin, Germany

Patients with diabetes mellitus are prone to infections. The reasons for this propensity are imperfectly defined. Ma et al. [1] in this issue suggest that defective macrophage function could be responsible. They studied F4/80-positive macrophages in spleen and peritoneal exudates of mice made them diabetic with streptozotocin. The macrophage number in the diabetic mice was reduced. Their immunogenic properties and nonopsonic phagocytosis to allogenic T cells were reduced. The antigen-presenting capacity of F4/80-positive macrophages from peritoneal exudates was also impaired. F4/80 is the cell surface target of a monoclonal antibody directed against mouse macrophages that was developed over 20 years ago by Austyn and Gordon [2]. The F4/80 molecule is expressed on macrophages, Kupffer cells, and microglial cells in the brain. The antigen has epidermal growth-factor-like domains connected to a C-terminal seven transmembrane region, placing it within the superfamily of G-protein-coupled receptors. The F4/80 molecule has a role in antigen-specific tolerance induction; however, its ligands and signaling mechanisms are not yet defined [3]. A brief review of what these wondrous macrophages do is in order.

Macrophages (Greek: "big eaters," from makros "large" + phagein "eat") are cells within the tissues that originate from monocytes (Fig. 1). Monocytes and macrophages are phagocytes, acting in both nonspecific defenses or "innate" immunity and specific acquired defenses. Macrophages phagocytose, that is engulf and then digest, cellular debris and pathogens either as stationary or mobile cells. Macrophages also serve to stimulate lymphocytes and other immune cells to respond to pathogens. When a monocyte enters damaged tissue through the endothelium of a blood vessel, a process known as the leukocyte adhesion cascade, the monocyte undergoes a series of interferon-gamma-mediated changes to become a macrophage. Monocytes are attracted to injury sites by chemical mediators through chemotaxis, triggered by a range of stimuli including damaged cells, pathogens, histamine released by mast cells and basophils, and chemokines and cytokines released by macrophages already at the site. Unlike short-lived neutrophils, the life span of a macrophage ranges from months to years.

Removing dead cell material is important in acute and chronic inflammation. Neutrophils and macrophages both express the cluster of differentiation molecule-31 (CD-31) also called platelet endothelial cell adhesion molecule 1. Neutrophils that are healthy can signal this state of affairs to the macrophage. However, if they are not and have phosphatidyl serine on their plasma membranes, they are scheduled for digestion. The removal of microparticles and necrotic tissue is to a greater extent handled by fixed macrophages, which will stay at strategic locations such as the lungs, liver, neural tissue, bone, spleen, and connective tissue. When a macrophage ingests a pathogen, the pathogen becomes trapped in a food vacuole, which then fuses with a lysosome. Within the lysosome, enzymes and toxic peroxides digest the invader. Macrophages can digest more than 100 bacteria before they finally die due to their own digestive compounds.

Macrophages are versatile cells that play many roles. As scavengers, they rid the body of worn-out cells and other debris. As secretory cells, monocytes and macrophages are vital to the regulation of immune responses and the development of inflammation; they churn out an amazing array of powerful chemokines, cytokines, enzymes, complement proteins, and regulatory factors. At the same time, they carry receptors for lymphokines that allow them to be "activated" into single-minded pursuit of microbes and tumor cells. After digesting a pathogen, a macrophage will present the antigen of the pathogen to a corresponding helper T cell. The macrophage presents the antigen by integrating it into the cell membrane and displaying it attached to a major histocompatibility complex (MHC) class II molecule, indicating to other white blood cells that the macrophage is not a pathogen, despite having antigens on its surface. Eventually, the antigen presentation results in the production of antibodies that attach to the antigens of pathogens, making them easier for macrophages to adhere with their cell membrane and conduct phagocytosis.

The antigen presentation on the surface of infected macrophages (in the context of MHC class II) in a lymph node stimulates type 1 helper T cells (TH1) to proliferate (mainly due to interleukin 12 secretion from the macrophage). When a B cell

in the lymph node recognizes the same unprocessed surface antigen on the bacterium with its surface-bound antibody, the antigen is endocytosed and processed. The processed antigen is then presented in MHCII on the surface of the B cell. The TH1 cells that have proliferated recognize the antigen MHCII complex (with costimulatory factors—CD40 and CD40L) via their T cell receptor and cause the B cell to produce antibodies that help opsonization of the antigen so that the bacteria can be better cleared by phagocytes.

Macrophages provide yet another line of defense against tumor cells and body cells infected with fungus or parasites. Once a T cell has recognized its particular antigen on the surface of an aberrant cell, the T cell becomes an activated effector cell, releasing chemical mediators known as lymphokines that stimulate macrophages into a more aggressive form. These activated or “angry” macrophages can then engulf and digest affected cells much more readily. The angry macrophage does not generate a response specific for an antigen but attacks the cells present in the local area in which it was activated.

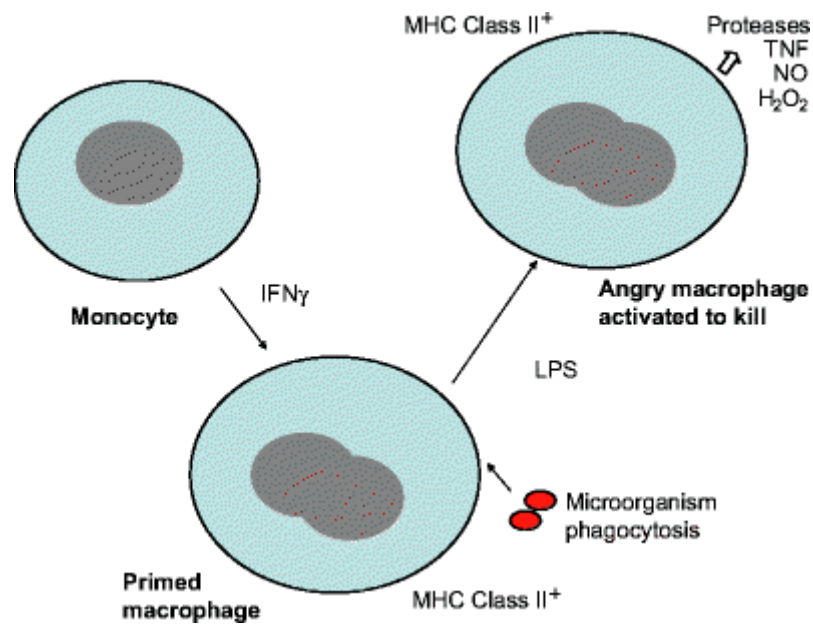
We cannot live without our macrophages. However, questions remain whether or not they should be manipulated under certain circumstances. Oh et al. [4] studied the fractalkine receptor (CX3CR1) that is expressed on injured endothelial cells and serves as an attractant for macrophages. Inhibiting fractalkine ameliorated ischemia-reperfusion renal injury. Furthermore, poisoning macrophages with clodronate-laden liposomes can specifically deplete the cells. Macrophage depletion also ameliorated renal ischemia-reperfusion injury in this model. However, in a similar renal ischemia-reperfusion injury study, macrophage depletion led to inability of the injured kidney to conduct repair [5]. Repair mechanisms are absolutely essential for recovery. Thus, manipulating macrophages may give very diverse results depending upon the inflammatory milieu. Ma et al. observed different effects on splenic macrophages and peritoneal macrophages in their diabetic model [1]. The antigen-presenting capacity of peritoneal macrophages appeared particularly impaired. These findings may be related to differences in the microenvironment surrounding the cells. Whether or not the microvasculopathy accompanying diabetes is a manifestation of impaired repair remains to be seen. Suffice it to say, macrophages are unique immune cells whose effects extend beyond straightforward defensive activities.

## Corresponding Author

Friedrich C. Luft, luft@charite.de

## References

1. Ma H, Liu G, Ding W, Wu Y, Cai L, Zhao Y (2008) Diabetes-induced alteration of F4/80+ macrophages: a study in mice with streptozotocin-induced diabetes for long term. *J Mol Med*.
2. Austyn JM, Gordon S (1981) F4/80, a monoclonal antibody directed specifically against the mouse macrophage. *Eur J Immunol* 11:805–815.
3. Van den Berg TK, Kraal G (2005) A function for the macrophage F4/80 molecule in tolerance induction. *Trends Immunol* 26:506–509.
4. Oh DJ, Dursun B, He Z, Lu L, Hoke TS, Ljubanovic D, Faubel S, Edelstein CL (2008) Fractalkine receptor (CX3CR1) inhibition is protective against ischemic acute renal failure in mice. *Am J Physiol Renal Physiol* 294:F264–F271.
5. Vinuesa E, Hotter G, Jung M, Herrero-Fresneda I, Torras J, Sola A (2008) Macrophage involvement in the kidney repair phase after ischaemia/reperfusion injury. *J Pathol* 214:104–113.



► Fig.1. Two-stage activation of macrophages is shown. Resident and recruited macrophages require interferon gamma ( $IFN\gamma$ ) to become primed. Local stimuli, microbial products, and dying cells trigger surface changes and cytokine production such as tumor necrosis factor, as well as reactive oxygen species.