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Review

Different *Leishmania* Species Drive Distinct Neutrophil Functions

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Leishmaniases are vector-borne diseases of serious public health importance. During a sand fly blood meal, *Leishmania* parasites are deposited in the host dermis where neutrophils are rapidly recruited. Neutrophils are the first line of defense and can kill pathogens by an array of mechanisms. They can also form web-like structures called neutrophil extracellular traps (NETs) that can trap and/or kill microbes. The function of neutrophils in leishmaniasis was reported to be either beneficial by contributing to parasite killing or detrimental by impairing immune response development and control of parasite load. Here we review recent data showing that different *Leishmania* species elicit distinct neutrophil functions thereby influencing disease outcomes. Emerging evidence suggests that neutrophils should be considered important modulators of leishmaniasis.

Leishmaniases

Leishmania (L.) are protozoan parasites causing leishmaniases, a spectrum of vector-borne neglected diseases affecting over 150 million people worldwide with 350 million at risk in about 98 countries or territories [1]. There is an incidence of over 2 million new cases per year, with an estimate of 0.5 million cases of visceral leishmaniasis (VL) and 1.5 million of cutaneous leishmaniasis (CL). The parasites are transmitted to mammals upon the blood meal of infected female phlebotomine sand flies. The species of *Leishmania* infecting the host broadly determines the type of disease that will evolve. An estimated 20 different *Leishmania* spp. cause the three main clinical disease manifestations comprising the cutaneous, mucocutaneous, and visceral forms. Some *Leishmania* species cause CL, the most common form of the disease. CL is characterized by the presence of localized skin ulcers that, in immunocompetent individuals, are self-healing, leaving disfiguring scars over months to years depending on the infecting *Leishmania* species. Several years following infection with *Leishmania* species of the *Vianna* subgenus, mucocutaneous leishmaniasis (MCL) can develop. MCL is characterized by the migration of parasites to mucosal tissues of the mouth and upper respiratory tract, leading to partial or total tissue destruction. Infection with *Leishmania donovani* or *Leishmania infantum* causes VL, which is the least common form of the disease but can be fatal if left untreated. In VL, the parasites migrate and replicate in lymphoid organs including the spleen, liver, and bone marrow, eventually leading to organ malfunction. No satisfactory treatment that is affordable, efficacious, easy to administer, and with low toxicity is currently available. Resistance against each of the drugs presently in use has been reported (reviewed in [2]). In addition, no vaccine is currently available; thus better understanding of the immune response that occurs following infection with the various *Leishmania* species is required to better target immunopreventive approaches.

Trends

Neutrophils are massively recruited following infection with *Leishmania* parasites. Neutrophils are well known for their microbicidal properties; however, some *Leishmania* parasites are able to escape killing.

The impact of neutrophils on leishmaniases remains not well understood. Emerging data suggest that neutrophils play a crucial role in the development of the different forms of the disease.

Studies in animal models revealed that neutrophils may play protective or deleterious roles at the onset of *Leishmania* infection. Recent models of neutropenic mice offer new tools to investigate the mechanisms involved in these processes.

Parasite and host factors appear to direct neutrophil effector function as well as neutrophil immunomodulatory function.

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The early events occurring at the site of infection are thought to be critical in the development of an efficient protective immune response against *Leishmania* infection. Special attention has been given to neutrophils, as these cells are among the first cells massively recruited to the site of infection [3–5]. In this review we discuss recent developments in the field with an emphasis on recent findings demonstrating that distinct *Leishmania* spp. specifically impact neutrophil function, with direct consequences on disease development.

Study of the Crosstalk between Neutrophils, Parasites, and Neighboring Cells

Neutrophils are innate immune cells mobilized from the bone marrow that migrate via the blood to areas of trauma or infection. They play a crucial role in the elimination of many invading pathogens [6,7]. Neutrophils can kill microbes using several mechanisms including the release of their toxic granule content in the local environment or in the **phagosome** (see Glossary) and via the formation of fibrous structures called **NETs**. NETs can trap pathogens and sometimes kill them through the toxicity of **histones** and/or antimicrobial granule-derived proteins associated with these structures [8]. Neutrophil effector functions need to be tightly regulated, as excessive activity can lead to tissue destruction and ultimately chronic inflammation [9]. In addition to these killing functions, increasing evidence supports a role for neutrophils in the modulation of innate and adaptive immune responses. This can be through the release of cytokines [10] or of other factors such as **eicosanoids** (thromboxane A2) that lead to dampening of the immune response by acting on T cells [11]. Crosstalk with other cells present at the site of infection or within the draining lymph nodes, including dendritic cells (reviewed in [12,13]), natural killer (NK) cells [14], and B cells [15], as well as sequestration of antigens [16,17] may also modulate the immune response in positive or negative ways.

Most of our current understanding of the role of neutrophils in leishmaniasis has been obtained by work performed in experimental mouse models. Although results from these studies provide important insights, they cannot always be extrapolated to humans as there are significant differences between human and murine neutrophils. While in human blood 50–70% of all leukocytes are neutrophils, they represent only 10–25% of leukocytes in murine blood [18,19]. Furthermore, the antimicrobial molecules present in human and mouse neutrophil granules differ. For instance, murine neutrophils do not express **defensins** or **azurocidin**, while these proteins are abundantly present in human neutrophils (reviewed in [20]). Assessing the function of human neutrophils in *Leishmania* infection has been difficult for several reasons. First, most experiments performed with human neutrophils are conducted using peripheral blood cells, as these cells are the most accessible in patients. However, blood neutrophils may not behave in the same way as neutrophils present at the site of infection (reviewed in [21]). For instance, no difference in **arginase** activity was observed in neutrophils isolated from the peripheral blood of healthy or infected individuals. By contrast, the arginase activity of neutrophils isolated from skin biopsies was found to be significantly increased in CL patients compared with that observed in biopsies of healthy patients [22]. Second, it is well established that host factors play important roles in disease development in leishmaniasis. The impact of *Leishmania major* LV39 on neutrophils from mice of the C57BL/6 or BALB/c genetic background was shown to differ dramatically regarding cytokine release and disease outcome [5,23,24]. The comparability of data obtained from samples from different patients may thus be complicated by genetic background, age, sex, lifestyle, and comorbidities [25], a point also valid for other diseases. This complexity stresses the need to obtain more insights on the role of neutrophils during human leishmaniasis.

Recruitment of Neutrophils to the Site of *Leishmania* Infection

The presence of neutrophils throughout the *Leishmania* life cycle is shown in Figure 1 (Key Figure). Rapid and massive neutrophil recruitment following needle inoculation of a high

Glossary

Amastigote: non-motile intracellular stage of *Leishmania* spp. that replicates within macrophages of the infected mammalian host.
Arginase: an enzyme that catalyzes the hydrolysis of L-arginine to ornithine and urea. It limits the L-arginine that is available for the synthesis of nitric oxide and contributes to immune regulation.
Azurocidin: multifunctional inflammatory mediator present in human neutrophil granules. It has bactericidal functions.
CD11b: surface molecule expressed on myeloid cells.
Defensin: small, cysteine-rich proteins found in animals and some plants with bactericidal and fungicidal properties. In humans they can be found in the azurophilic granules of neutrophils, in the Paneth cells of the small intestine, and in various types of epithelial cells.
Eicosanoid: molecules derived from 20-carbon fatty acids that have immune-modulatory effects.
GP63: metalloprotease that is abundantly expressed on the surface of promastigotes of many *Leishmania* spp. and is considered a virulence factor.
Granulopoiesis: formation of granulocytes in blood-forming tissues, which under physiological conditions are located in the bone marrow. The emergence of granulocytes occurs via several precursors, such as myeloblasts, promyelocytes, myelocytes, and metamyelocytes.
Granzmye B: important component of granules in cytotoxic lymphocytes and NK cells that induces cell death on entrance into target cells by caspase activation and mitochondrial permeabilization.
Histone: protein found in eukaryotic cells that envelopes and structures DNA. It is the main component of chromatin.
Human neutrophil elastase quantitation: measurement of the concentration of human neutrophil elastase in supernatants of cell suspensions by the addition of a fluorogenic substrate and measurement of the resulting fluorescence intensity.
Lipophosphoglycan (LPG): a surface molecule and virulence factor abundantly present on the surface of *Leishmania* spp.

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