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Acidic Microenvironments Found in Cutaneous Leishmania Lesions Curtail NO-Dependent Antiparasitic Macrophage Activity

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Abstract:

Local tissue acidosis affects anti-tumor immunity. In contrast, data on tissue pH levels in infected tissues and their impact on antimicrobial activity is sparse. In this study, we assessed the pH levels in cutaneous Leishmania lesions. Leishmania major-infected skin tissue displayed pH levels of 6.7 indicating that lesional pH is acidic. Next, we tested the effect of low extracellular pH on the ability of macrophages to produce leishmanicidal NO and to fight the protozoan parasite Leishmania major. Extracellular acidification led to a marked decrease in both NO production and leishmanicidal activity of lipopolysaccharide (LPS) and interferon γ (IFN- γ)-coactivated macrophages. This was not directly caused by a disruption of NOS2 expression, a shortage of reducing equivalents (NAPDH) or substrate (L-arginine), but by a direct, pH-mediated inhibition of NOS2 enzyme activity. Normalization of intracellular pH significantly increased NO production and antiparasitic activity of macrophages even in an acidic microenvironment. Overall, these findings indicate that low local tissue pH can curtail NO production and leishmanicidal activity of macrophages.

Keywords: pH, Leishmania, macrophages, NO, NOS2