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ISID Small Grants Program Final Report

by Silvia Correa, PhD • Argentina

Study of the mechanisms of weight loss, anorexia and hepatic injury in *Candida albicans* infection under stress conditions

Infection is associated with negative energy balance, with reduced food intake, weight loss, increased thermogenesis, and fever. Decreased caloric intake belongs to an endogenous protection mechanism that allows the organism to optimize the immune/inflammatory reactions. A complex network of pro-inflammatory cytokines released during infection, hormones, and low-molecular weight mediators coordinates in periphery multiple biochemical and metabolic changes that in turn provide an important negative feedback to cytokine production and toxicity. Leptin, the 16-kDa protein product of the *ob* gene, is an important regulator of the energy balance. Involved in the acute phase response, leptin increases sharply after infection and its production resembles that of pro-inflammatory cytokines. Interestingly, endogenous leptin plays a protective role against TNF induced lethality suggesting immunomodulatory and anti-inflammatory effects. We are working with a model of candidiasis and stress developed by intraperitoneal infection with 3×10^8 blastoconidia of *C. albicans* followed by chronic varied stress exposure during five days. Rats show an accelerated impairment of the innate immune response as well as signs of hepatic injury that include hyperplasia of Kupffer cell, steatosis, increased β -oxidation of fatty acids,

release of the enzymes glutamic oxaloacetic transaminase [SGOT] and glutamyl transpeptidase [GGTP] and alterations in the lipid profile (cholesterol, triglycerides and lipoprotein levels). After 3 days of stress and infection rats have in serum reduced levels of IL-6, glucose and leptin but exhibit increments in corticosterone. In liver, the levels of the cytosolic signal transduction and activator of transcription protein (STAT), phosphorylated STAT-3 involved in signaling through receptor coupled gp 130, is also reduced. Our goal is to establish a possible mechanism by which the simultaneous exposure to *Candida albicans* infection and stress triggers the metabolic alterations. More specifically we are aimed to (i) Elucidate the contribution of leptin to the impairment of the innate control of the infection; (ii) Determine the involvement of corticosterone in the progression of liver injury; (iii) Characterize homeostatic mechanisms operating after infection but deficient following stress exposure. ❖

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