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43. Macrophage cytostactif effect on trypanosomes is mediated by nitric oxide from L-arginine.

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Macrophages play a key role in the control of protozan parasites. In trypanosomiasis, marked increases in macrophagic cell number and cell activation are observed. Recent reports demonstrate the importance of a previously unknown biochemical pathway synthesizing nitrogen oxides from L-arginine in activated macrophage-mediated antitumoral and antimicrobial activities.

The role of nitrogen oxides in macrophage effector mechanisms against trypanosomes are first investigated on *Trypanosoma musculi*, a natural parasite of the mouse and then on *Trypanosoma brucei gambiense*, *T. b. rhodesiense* and *T. b. brucei*.

Peritoneal macrophages from the 10th day of *T. musculi* infection are activated (increases in endocytosis and la expression; H_2O_2 production) and, unlike resident macrophages, do not favor *in vitro* parasite multiplication. Nitrite production by macrophages is maximum around the 14th day of infection and parallels development of macrophage trypanostatic activity. Macrophages from BCG-infected mice or treated with IFN-γ *in vitro* also exert a trypanostatic activity. Trypanostatic activity is suppressed by N^G monomethyl-L-arginine (N^GMMA), a specific inhibitor of the biochemical pathway synthesizing nitrogen oxides from L-arginine. Nitric oxide (NO), alone, inhibited parasite proliferation whereas NO_2 has no effect.

In vitro multiplication of *Trypanosoma brucei gambiense* (ITMAP 1841 and FEO strains), *Trypanosoma brucei brucei* (ANTAT 1.1) in presence of resident murine peritoneal macrophages is inhibited by *in vitro* macrophage activation with IFN-γ. This inhibitory effect is suppressed by N^GMMA. Treatment with nitric oxide inhibits *in vitro* trypanosome proliferation whereas NO_2 has no effect. A marked increase in animal survival is observed when mice are injected with NO-treated trypanosomes (*T. b. gambiense*, *T. b. brucei* or *T. b. rhodesiense* (LOPO strain)).

As reported for intracellular parasites (*Leishmania major* and *Toxoplasma gondii*) all these data show that the L-arginine : NO metabolic pathway is involved in the macrophage effector mechanisms against extracellular trypanosomes. Moreover, NO, the effector molecule, alone, has a direct powerful trypanostatic activity. Further studies on the mechanism of the trypanostatic activity of NO reveal the role of iron which can reverse the effects of NO.

Further studies on all steps of effector mechanisms involved in trypanosomiasis, and especially the L-arginine : NO biochemical pathway, might provide information for new therapeutic approaches.

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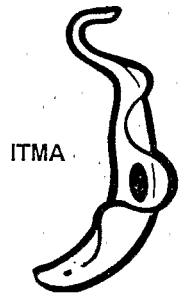

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