# PHAGOCYTOSIS AND IFN-γ-MEDIATED SIGNALING AT MATERNAL FETAL INTERFACE

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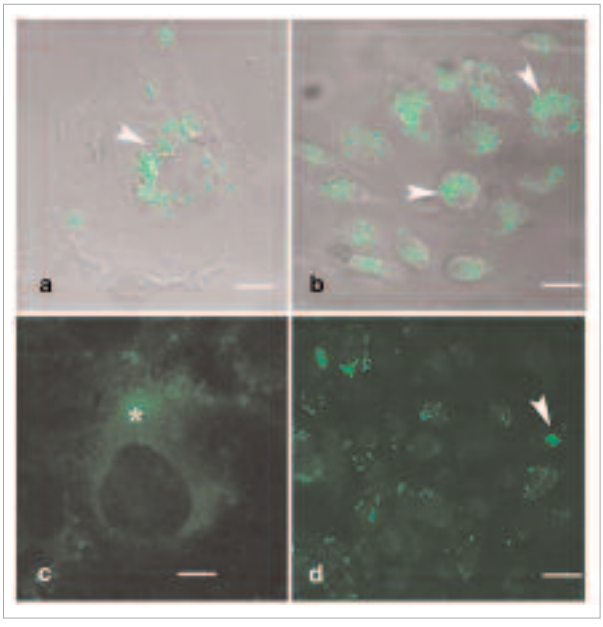


*Trophoblast and GFP-E. coli in IFN-γ-treated cultures*

In many species, phagocytosis is a remarkable characteristic exhibited by implanting and post-implanting trophoblast cells. Particularly in mice, during the first half of the gestation, giant trophoblast cells phagocytize maternal endometrial cells and among them, blood cells, which may have a role in nutrition and acquisition of space for embryo development. Throughout gestation, however, phagocytosis of microorganisms can also be experimentally observed. In relation to the phagocytic activity, trophoblast cells and macrophages share in common several characteristics, such as reactive oxygen species production, C3b-mediated phagocytosis, production of nitric oxide, and both those cell types increase their potential for phagocytosis in the presence of IFN-γ. In macrophages, IFN-γ is a potent regulatory molecule for phagocytosis and able to suppress the synthesis of cytoplasmic proteins involved in viral replication, to activate the transcription factor NF-KB involved in the inflammatory defense response and to induce the production of nitric oxide and oxidases responsible for reactive oxygen species formation. On the other hand, IFN-γ produced by immune and non-immune cells is present in the materno-fetal interface and is considered a physiological component of gestation. However, under conditions in which the immune/inflammatory response against pathogens prolongs non-physiological concentrations of IFN-γ in the maternal organism, pregnancy may be affected. So, considering that phagocytosis is an inherent activity of trophoblast cells, which can be related to defense functions, this study aims to determine the concentrations of IFN-γ in normal gestation and in pregnant remates challenged with LPS; to determine the maximum IFN-γ concentration that does not interfere with the gestation progression; to establish *in vivo* and *in vitro* models that allow the study of the process of phagocytosis of microorganisms or part of them by trophoblast cells; to evaluate the action of IFN-y on the gene expression of trophoblast cells and mainly, on the expression of nitric oxide synthase, by using DNA macroarray approaches.

## SUMMARY OF RESULTS TO DATE AND PERSPECTIVES

Trophoblast phagocytosis is an event of fundamental importance for the pregnancy. It takes place in early gestation, and is crucial for the embryo nutrition, iron uptake, acquisition of space, and protection against microorganisms and, very likely, is also crucial for the elaboration of a specific immune response at the maternal-placental interface rather than for directly destroying pathogens. In macrophages, IFN-γ is able to mediate antiviral effects through the expression of a large panel of cytokines directly associated with the innate and adaptive immunity and to induce a number of processes to activate phagocytosis. Recently it has been found that IFN-γ is produced by uterine NK cells, coincidently with the period, in which the mouse trophoblast exhibits high phagocytic activity. Our hypothesis is that physiological IFN-γ is one of the central regulators of the gestational homeostasis. Exposure of mouse embryos to IFN-γ definitively showed the potential of this cytokine for inducing phagocytosis of microorganisms in trophoblast cells. IFN-γ-mediated response involved the expression of nitric oxide synthase (NOS) and NADH-oxidase enzymatic complexes and, respectively, the release of nitric oxide and reactive oxygen species, all of which are able to damage various biological molecules. The release of NO may also indicate a relevant role in the pro-inflammatory activity at the maternal fetal interface. The expression of inducible NOS at the transcriptional level was a JAK/STAT1-dependent pathway that significantly decreased upon pharmacological inhibition of IFN-γ receptor phosphorylation. The antioxidant balance in stimulated trophoblast was also verified. Through gene and protein expression, the activity of trophoblast oxidative enzymes was shown to be able to promptly compensate the secretion of reactive species. Furthermore, cDNA macroarray and RT-PCR showed that at least 7 genes are prominently upregulated in the presence of IFN-γ. These results not only suggest that IFN-γ for long considered as an abortifacient molecule may play physiological functions during the gestation by regulating trophoblast phagocytosis and expression of cytokines, but also contribute to understanding important roles of trophoblasts.

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