

## The Effect of *R. conorii* and Israeli Spotted Fever on Secretion O + Factors from Macrophages

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The Mononuclear phagocytes act as effective microbicidal host defense cells against many pathogenic microorganisms. They have been implicated in regulating the functions of lymphoid and hematopoietic cells, and, in most cases, these effects are mediated by soluble factors such as prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), tumor necrosis factor (TNF) and interleukin-1 (IL-1), produced by circulating monocytes and tissue macrophages (Nathan, 1987). In this study we examined in an in vitro system PGE<sub>2</sub> and TNF production by MdM infected with *Rickettsia conorii* (RC, Casablanca strain), or Israeli spotted fever (ISF, G-212 strain). We also examined the effect of dexamethasone on A. rickettsial yield in MdM and B. PGE<sub>2</sub> and TNF production by MdM rickettsiae infected MdM.

RC and ISF were found to induce human MdM to produce TNF alpha, which increased when a higher multiplicity of infection of rickettsiae was used. The capability of rickettsiae to induce TNF production from macrophages is not unique to rickettsiae, but has recently been demonstrated in a wide range of intracellular pathogens such as viruses (Aderka *et al.*, 1985, ), bacteria (Blanchard *et al.*, 1987; Havell, 1987; Leist *et al.*, 1988), eucaryotic parasites (Bate *et al.*, 1988) and fungi (Djeu *et al.*, 1988). Various molecules have also been found to be able to induce TNF in macrophages, such as bacterial lipopolysaccharides and endotoxin component responsible for the induction of TNF alpha in human macrophages.

Recently we have shown that TNF alpha inhibits rickettsial growth in HEp-2 cells; the inhibition is enhanced by gamma-interferon (Manor and Sarov, 1990). This suggests that *in vivo*, early in the rickettsial infection, TNF may play a protective role. However, it is also possible that TNF might cause some of the pathological effects seen later in the course of rickettsial infection (Beutler and Cerami, 1988).

RC and ISF also induced human MdM to produce PGE<sub>2</sub>. The level of PGE<sub>2</sub> increased when a higher multiplicity of infection of rickettsiae was used. PGE<sub>2</sub> has been shown to be produced by macrophages infected with viruses (Laegreid *et al.*, 1989; Laegreid *et al.*, 1989b), bacteria (Molvig *et al.*, 1988; Nichols *et al.*, 1988; Nichols *et al.*, 1987), and intracellular parasites (Clark and Hunt, 1986; Reiner *et al.*, 1988), and may cause profound metabolic and functional changes in these cells (Chouaib and Bertoglio, 1988).

It has been found that in ascites from mice lethally infected with *R. tsutsugamushi* the levels of PGE<sub>2</sub> increased, and that inflammatory macrophages from lethally infected mice produced from two to five times more PGE<sub>2</sub> than an equivalent number of cells from resistant mice. The former macrophages failed to express Ia antigen even after treatment with gamma interferon . Incubation of

macrophages from susceptible animals with indomethacin resulted in partial, but not complete, restoration of Ia antigen expression (Jerrells, 1988). Experiments are in progress to examine the effect of RC and ISF rickettsiae infection on Ia antigen expression in human macrophages.

Dexamethasone inhibited TNF and PGE<sub>2</sub> production. These results are in agreement with those described by Beutler *et al.*, 1996 and Danon *et al.*, 1978, respectively, who have shown that dexamethasone inhibits TNF and PGE<sub>2</sub> at the transcriptional level.

Both RC and ISF were found to replicate in MdM. Treatment of the cells with dexamethasone enhanced the yield of infectious rickettsial particles in these cells. These results cannot be simply explained by the dexamethasone inhibition of TNF production from rickettsial infected MdM. This conclusion is based on the findings that addition of an excess of PGE<sub>2</sub>, which inhibits TNF production, or indomethacin, which enhances TNF production, did not affect the rickettsial yield in MdM. The mechanism by which dexamethasone enhances rickettsial yield in MdM needs further investigation. Corticosteroids have been found to enhance replication of viruses (Tanaka *et al.*, 1984), and the intracellular parasites (Bushell and Hobson, 1978; Yang *et al.*, 1983; Woodman *et al.*, 1979).

The level of TNF detected in the medium of the RC or ISF infected MdM reached a maximum at 24 hpi and then declined. When the infected MdM were washed daily, the TNF level remained high throughout the entire experimental period. A possible explanation is that the high level of PGE<sub>2</sub> depressed TNF production, and that washing of the cells eliminated the interference of PGE<sub>2</sub>. Kunkel *et al.*, (1988) have shown that PGE<sub>2</sub> regulates macrophage derived TNF gene expression. These observations support the suggestion that TNF and PGE<sub>2</sub> regulates macrophage derived TNF gene expression. These observations support the suggestion that TNF and PGE<sub>2</sub> may affect each other's production (Dayer *et al.*, 1985; Lehmann *et al.*, 1988). TNF produced by activated macrophages may be responsible for increased synthesis of PGE<sub>2</sub>, which, in turn, limits macrophage activation in an autoregulatory manner (Laegreid *et al.*, 1989a; Laegreid *et al.*, 1989b). A delicate balance between TNF and PGE<sub>2</sub> produced by macrophages might play a major role in the outcome and severity of rickettsial infection *in vivo*. This study was supported by NIH-NIAID Contract No. AI 68010.

Dedicated to the memory of Professor Israel Sarov, an exemplary scientist and teacher.

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