FASL UPREGULATION AND T CELL DEATH BY AICD ARE PREVENTED BY MACROPHAGE- AND DC-DERIVED PGE2

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T cell activation/differentiation is driven by interactions with antigen presenting cells (APCs). Little is known about the regulation of activated T cell survival by APC-derived soluble molecules. Macrophage cell lines, adherent peritoneal exudate cells (PECs) and dendritic cells (DCs) were cultured for 24h in the presence or absence of LPS and the resulting supernatants were added to the T cell hybridoma DO11.10 during stimulation with anti-CD3 antibodies (activation-induced cell death; AICD). Apoptosis was determined by flow cytometry and gene expression analyzed by RT-PCR. APC-derived supernatants were able to suppress AICD and this effect was greater in LPS-stimulated samples. Using different KO mice, we found that LPS induction of the suppression factor is dependent of TLR4 and MyD88 and independent of CD14 and IRF3. Indomethacin-treatment of APCs diminished the inhibitory activity of the supernatants and recombinant prostaglandin E2 (rPGE2) was also capable of suppress AICD. Supernatants and PGE2 prevented FasL upregulation in DO11.10 cells in response to anti-CD3. Neither supernatants nor rPGE2 protected DO11.10 cells from agonistic anti-Fas antibodies. Taken together, these results indicate that APCs can modulate activated T cell survival by releasing PGE2 in response to LPS via a TLR4/MyD88-dependent mechanism. PGE2, in turn, interferes with anti-CD3-mediated apoptosis by preventing FasL upregulation.

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