A94 - Reduced atx levels protect mice from lps-induced endotoxemia

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Introduction:
Autotaxin (ATX, Enpp2) is a secreted enzyme present in biological fluids that catalyses the production of lysophosphatidic acid (LPA). LPA is a bioactive phospholipid evoking various cellular responses in most cell types. Upreregulated ATX levels have been reported in various chronic inflammatory diseases. Given the established role of LPA in the inflammatory response, we investigated a possible role for the ATX/LPA axis in LPS-induced endotoxemia.

Methods:
LPS was injected intraperitoneally (20 mg/kg) in mice producing 50% ATX levels (ATX^{df/+}, heterozygous null mutant mice), in mice producing 20-30% reduced ATX levels upon inducible inactivation (R26CreER^{T2}/Enpp2^{n/n} mice) and in mice expressing 150-200% increased ATX levels (Enpp2-Tg mice). Kaplan-Meier survival analysis was performed. ATX activity was measured using the TOOS activity assay.

Results:
ATX^{df/+} mice that produce almost 50% reduced serum ATX levels show increased survival compared to their littermate controls. For the inducible inactivation of ATX, Enpp2^{n/n} targeted mice were crossed with the R26CreER^{T2}/Enpp2^{n/n} mice and tamoxifen induction enabled temporal control of floxed gene expression. R26CreER^{T2}/Enpp2^{n/n} mice were more protected against LPS-induced endotoxemia compared to control mice. Enpp2-Tg mice overexpressing autotaxin and showing a 2-fold increase in plasma levels do not display improved survival rates compared to control group.

Conclusion:
ATX participates in systemic inflammation, as reduced ATX levels in circulation decrease lethality of mice from caused by LPS. The excess amount of circulating ATX does not exacerbate the systemic inflammatory response to LPS.