A148 PRODUCTION AND BIOLOGICAL ROLE OF HEPATOCYTE AND MYELOID CELL-DERIVED INTERLEUKIN-1 RECEPTOR ANTAGONIST IN A MODEL OF SYSTEMIC INFLAMMATION

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Background Interleukin-1 receptor antagonist (IL1Ra) is a specific IL1 inhibitor that possesses anti-inflammatory activities in experimental models and in patients. Interestingly, administration of IL1Ra, particularly in animal models, can ameliorate the physiological consequences of septic shock. The contribution of the IL1/IL1Ra balance during endotoxaemia was confirmed by the high susceptibility of IL1Ra deficient mice to a lethal dose of lipopolysaccharide (LPS). Previous in vitro data demonstrated that both hepatocytes and myeloid cells produce IL1Ra in large amounts in response to LPS.

Objectives The aim of this study was to determine the role of hepatocyte- and myeloid cell-derived IL1Ra in the production of circulating IL1Ra and in the control of survival in response to endotoxin in vivo.

Methods Conditional knockout mice in which IL1Ra production has been specifically targeted in hepatocytes (IL1RadeltaH), myeloid cells (IL1RadeltaM) or in both cellular sources (IL1RadeltaH+M) were generated in a pure C57BL/6 genetic background by using the LoxP/Cre-recombinase system. Systemic inflammation was induced by intraperitoneal (ip) injection of 10 mg/kg LPS in IL1RadeltaH, IL1RadeltaM, IL1RadeltaH+M and control mice. IL1Ra was quantified by ELISA in different organs and sera 4 or 18 h after injection. LPS (10 mg/kg) was also injected ip in the different conditional IL1Ra knockout mouse lines as well as in constitutively IL1Ra knockout (IL1Ra–/–) and control mice for a survival test.

Results The levels of circulating IL1Ra were decreased by 15% and 57% in IL1RadeltaH and IL1RadeltaM mice, respectively, 4 h after LPS administration compared with control mice. IL1Ra levels were very low in the circulation of IL1RadeltaH+M mice (decreased by 92% and 75% 4 h and 18 h after LPS injection, respectively). In addition, IL1Ra levels were decreased by 56%, 20% and 76% in the livers of IL1RadeltaH, IL1RadeltaM

and IL1RadeltaH+M mice, respectively, in response to LPS. We observed a strong decrease of IL1Ra levels in the spleen (70%) and lung extracts (50%) in both IL1RadeltaM and IL1RadeltaH+M mice versus control mice. Finally, IL1Ra–/–, IL1RadeltaM and IL1RadeltaH+M mice were more susceptible than control mice to the lethal effects of endotoxin, whereas IL1RadeltaH mice exhibited a similar lethality profile as control mice.

Conclusions We showed that (1) hepatocytes and myeloid cells are the two major cellular sources of hepatic and circulating IL1Ra in response to LPS; (2) myeloid cells represent an important source of IL1Ra in the spleen and lung after LPS challenge; (3) IL1Ra production by myeloid cells, but not hepatocytes, is critical for survival during endotoxaemia.