A20 MSU, THE ADJUVANS OF DYING CELLS ACTIVATES THE NALP3 INFLAMMASOME BY SODIUM OVERLOAD

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Background and objectives Monosodium urate (MSU) is one of the endogenous danger molecules generated during apoptosis. Precipitated MSU crystals in tissues and joints induce an inflammatory process with interleukin 1 β (IL-1β) induction after NALP3 inflammasome (NALP3i) activation resulting in gouty arthritis. However, the exact mechanism of NALP3i activation is still elusive. The goal is the identification of the mechanism of NALP3i idependent IL-1β production induced by MSU crystals.

Materials and methods Uptake of MSU was analysed by time lapse microscopy and cytofluorometry. Via REM-EDX the morphological and chemical structure of urate crystals was identified. The relative intracellular sodium concentration was analysed by Sodium Green fluorescence. The human IL-1β induction in presence of inhibitors of lysosomal acidification and of aquaporins in culture supernatants was quantified by ELISA. Additionally, mice were treated i.p. with chloroquine

following injection of MSU in generated air pouches. IL-1β production in the pouch fluid was quantified.

Results Blood borne phagocytes ingest MSU crystals and substantially increase their side scatter reflecting increased 'granularity'. After the uptake of the crystals the cells swell shown by augmented forward scatter and time-lapse microscopy. Most of the phagocytes show an intact plasma membrane after ingestion of crystals. Incubation of phagocytes with MSU results in an induction of IL-1β production. Needle-shaped MSU crystals release sodium after treatment with acidic milieu and switch into barrel-shaped crystals. In swollen cells the intracellular sodium concentration of phagocytes after the uptake of MSU displays a markedly increased intracellular sodium concentration. Furthermore, the inhibition of lysosomal acidification and of aquaporins results in reduction of IL-1β production in in vitro and in vivo.

Conclusions We suggest a novel model of NALP3i activation after phagocytosis of MSU crystals: the phagocytes ingest crystals into endosomes resulting in fusion with acidic lysosomes. That induces a massive release of sodium from the MSU crystal and enhances the intracellular osmolarity. The hyperosmolarity of the cell is compensated by passive water influx through aquaporins following cell swelling. The latter reduces the intracellular potassium concentration below the threshold of NALP3i activation. Finally, the decreased IL-1β production by treatment with inhibitors of lysosomal acidification or inhibitors of aquaporins supports our new model of inflammasome activation by MSU.