Cystatin C-deficiency is associated with increased NLRP3 inflammasome activation and LPS-induced sepsis

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Cystatin C (encoded by CST3 on human chromosome 20p11.21) is a potent cysteine protease inhibitor that plays an important role in various biological processes including cancer, cardiovascular diseases and neurodegenerative diseases. It is ubiquitously expressed and secreted from various cell types and is abundant in body fluids. Inflammasomes are multimeric protein platforms that mediate activation of pro-inflammatory caspase-1 and maturation of pro-inflammatory cytokines such as interleukin-1β (IL-1β) and IL-18. Autophagy, an intracellular process important for recycling of damaged organelles and destruction of intracellular pathogens, was reported to protect the host from excessive inflammation. In the present study we demonstrated that cystatin C-deficient mice were significantly more sensitive to the lethal LPS-induced sepsis. We demonstrated that pro-caspase-11 and pro-IL-1β are up-regulated in cystatin C-deficient bone marrow-derived macrophages (BMDMs) upon LPS stimulation. We examined the role of cystatin C-deficiency in Nlrp3 inflammasome activation and release of pro-inflammatory cytokines in BMDMs upon LPS and ATP stimulation. Our results show that cystatin C-deficient BMDMs secrete higher amounts of pro-inflammatory cytokine IL-1β due to increased caspase-1 and -11 activation upon Nlrp3 inflammasome activation, but is not mediated by elevated activity of cysteine cathepsins. Cystatin C-deficient BMDMs show decreased levels of autophagy, which might lead to increased inflammatory response.