COMMD10 IS A NEGATIVE REGULATOR OF MONOCYTE-DRIVEN INFLAMMATION IN SEPSIS AND INFLAMMATORY BOWEL DISEASE

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COMMD proteins are considered as master regulators of NFkB. Here we investigated the role of COMMD10 in modulating the inflammatory function of effector monocytes and their macrophage descendants in sepsis and IBD. COMMD10-deficiency was targeted to myeloid cells (myeloidΔCommd10 mice). COMMD10-deficient BM-derived macrophages exhibited hyper-activation of NFkB and augmented production of its governed inflammatory mediators in response to LPS. In vivo, myeloidΔCommd10 mice developed more severe sepsis in response to LPS, resulting in elevated levels of inflammatory cytokines in serum concomitantly with hyper-activation of NFkB and NLRP3 inflammasome complex in affected organs. Moreover, intestinal barrier was breached in septic myeloidΔCommd10 mice, manifested by higher bacterial load in visceral organs and reduced levels of colonic tight junction proteins. Inducible ablation of Ly6C^hi monocytes in myeloidΔCommd10 mice improved barrier integrity and abolished the intensified septic response. COMMD10-deficient macrophages also exhibited impaired bactericidal activity. In a model of DSS-induced colitis, myeloidΔCommd10 mice exhibited aggravated colitis, manifested by higher colitis colonoscopy scores, shorter colon, lower survival rate and elevated levels of inflammatory cytokines in the colon and serum after 7 days. Conversely, at the initial inflammatory phase, there were significantly lower numbers of infiltrating Ly6C^hi monocytes and neutrophils with less local inflammation. However, IL-1β was increased in the serum of septic myeloidΔCommd10 mice and was reduced upon monocyte ablation. Collectively, our results highlight COMMD10 as a crucial regulator of monocyte-driven inflammation and bactericidal activity.