Osteopontin polymerization in systemic inflammatory response syndrome

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Osteopontin is a unique multifunctional matrix protein that plays roles in inflammation and immunomodulation in addition to tissue calcification. Osteopontin elevates its activity by thrombin-cleavage at the middle of the molecule, when the cryptic integrin binding site is exposed (Yokosaki Y, et al. J Biol Chem 274, 1999). On the other hand, osteopontin forms homopolymer catalyzed by a cross-linking enzyme, transglutaminase. Interestingly, polymeric osteopontin also forms binding site for the same integrin $\alpha_9\beta_1$ on the surface of the molecule (Nishimichi N, et al. J Biol Chem 284, 2009). Mediated by an interaction with this integrin, osteopontin attracts neutrophils (Nishimichi N, et al. J Biol Chem 286, 2011). These characteristics of osteopontin suggest that post-transcriptional modifications, enzymatic cleavage and a polymerization, are required for regulation of osteopontin functions. There are over 20 protease cleavage sites within an osteopontin molecule that consists of 298 amino acid residues by enzymes including MMPs, plasmin and cathepsin D besides thrombin. This protease-labile nature of osteopontin could be a limitation in function at the site of inflammation where multiple proteases are highly concentrated. Polymeric osteopontin, however, is protease-resistant and could exert its function for a longer period. Therefore, it is conceivable that pro-inflammatory function of osteopontin might be carried out mainly by polymeric osteopontin, which could exert temporally superior function and could induce protracted severe inflammation. In the present study, we observed effects of polymerization of osteopontin on systemic inflammatory syndrome by generating a monoclonal antibody, BOP-1, that inhibits the polymerization specifically. Administration of BOP-1 to LPS-induced systemic inflammatory response syndrome (SIRS) model mice 1) attenuated peritoneal influx of inflammatory cells and 2) decreased inflammatory cytokines, IL-6 and MCP-1 in serum. These results suggest a critical role of polymeric osteopontin in regulation of inflammation.