Novel Mechanisms in leukocyte homing in inflammation and tumor physiology

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Inflammation is characterized by the recruitment of leukocytes from the bloodstream. In mice, the rapid arrival of neutrophils is followed by a wave of inflammatory lymphocyte antigen 6 complex (Ly6C)-positive monocytes. In contrast $Ly6C^{low}$ monocytes survey the endothelium in the steady state, but their role in inflammation is still unclear. Using confocal intravital microscopy, we showed that upon viral Toll-like receptor 7/8 (TLR7/8)-mediated inflammation of mesenteric veins, platelet activation drives the rapid mobilization of $Ly6C^{low}$ monocytes to the luminal side of the endothelium. After repeatedly interacting with platelets, Ly6Clow monocytes commit to a meticulous patrolling of the endothelial wall and orchestrate the subsequent arrival and extravasation of neutrophils through the production of proinflammatory cytokines and chemokines. At a molecular level, we showed that cysteine-rich protein 61 (CYR61)/CYR61 connective tissue growth factor nephroblastoma overexpressed 1 (CCN1) protein is released by activated platelets and enables the recruitment of $Ly6C^{low}$ monocytes upon vascular inflammation. In addition endothelium-bound CCN1 sustains the adequate patrolling of $Ly6C^{low}$ monocytes both in the steady state and under inflammatory conditions. Blocking CCN1 or platelets with specific antibodies impaired the early arrival of $Ly6C^{low}$ monocytes and abolished the recruitment of neutrophils. These results refined the leukocyte recruitment cascade model by introducing endothelium-bound CCN1 as an inflammation mediator and by demonstrating a role for platelets and patrolling $Ly6C^{low}$ monocytes in acute vascular inflammation.

Monocyte diversity found in human also leads to complex roles in chronic inflammation and tumor physiopathology. We now have characterized human, non-classical $CD14^{dim}CD16^{+}$ patrolling monocytes as a proangiogenic subset supporting tumor growth. These monocytes were captured by the tumor vasculature stimulated by IFNγ or TNFα. They induced the chemokine CX3CL1 and led to continuous crawling of the proangiogenic monocytes along the endothelium, thus hampering extravasation. Transendothelial migration was initiated by simultaneous exhibition of cytokines and tumor derived angiogenic factors including VEGF. The recruited proangiogenic monocytes further boosted angiogenesis by secreting MMP-9, leading to release of more matrix bound VEGF. This cascade amplified the entry of angiogenic monocytes to the tumor and chronically inflamed tissue. This sets the stage for combined therapies with anti-angiogenic and IFNγ-based immunotherapy for solid tumors. In summary, we have defined new mechanisms that explain acute and chronic inflammation, the latter also applies to tumors.