Curtale G, Mirolo M, Renzi T, Rossato M, Bazzoni F, Locati M. Negative regulation of Toll-Like Receptor 4 signalling by the IL-10-dependent microRNA-146b. *Proceedings of the National Academy of Sciences of USA, in press.*

Toll-like receptors (TLRs) play key roles in detecting pathogens and initiating inflammatory responses that, subsequently, prime specific adaptive responses. Several mechanisms control TLR activity to avoid excessive inflammation and consequent immunopathology, including the anti-inflammatory cytokine IL-10. Recently, several TLR-responsive microRNAs (miRs) have also been proposed as potential regulators of this signaling pathway, but their functional role during the inflammatory response still is incompletely understood. In this study, we report that, after LPS engagement, monocytes up-regulate miR-146b via an IL-10-mediated STAT3-dependent loop. We show evidence that miR-146b modulates the TLR4 signaling pathway by direct targeting of multiple elements, including the LPS receptor TLR4 and the key adaptor/signaling proteins myeloid differentiation primary response (MyD88), interleukin-1 receptor-associated kinase 1 (IRAK-1), and TNF receptor-associated factor 6 (TRAF6). Furthermore, we demonstrate that the enforced expression of miR-146b in human monocytes led to a significant reduction in the LPS-dependent production of several proinflammatory cytokines and chemokines, including IL-6, TNF-α, IL-8, CCL3, CCL2, CCL7, and CXCL10. Our results thus identify miR-146b as an IL-10-responsive miR with an anti-inflammatory activity based on multiple targeting of components of the TLR4 pathway in monocytes and candidate miR-146b as a molecular effector of the IL-10 anti-inflammatory activity.