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Regulation of aberrant inflammatory responses and development of vascular disease through the IL-1RI co-receptor TILRR

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Members of the toll-like and IL-1 receptor family (TIR) are central regulators of immune and inflammatoryresponses. Signal activation is induced through ligand binding and controlled by system-specific co-receptors.We have identified a novel component of the IL-1receptor complex,the co-receptor TILRR (FREM-1isoform 2). TILRR associates with the signallingreceptor and magnifies IL-1induced activation of the transcription factor NF-κB by enhancing signalamplification at the level of the receptor complex and potentiate recruitment of the MyD88 adapter.TILRR-controlled MyD88 dependent activation is regulated in a Ras-dependent manner, reflected inalterations in cytoskeletal structure and cell adhesion, and in release of cytoskeletal bound IκBα. In *silico*simulations using agent based modeling of the NF-κB network predicts the cytoskeletal control of inhibitorlevels provides a mechanism for rapid signal calibration, and enables activation-sensitive regulation of NF-κBinducedinflammatory responses.Recent studies have used *in vivo* models to assess the role of TILRR in host defense, vascular diseaseand lung fibrosis. Results show that TILRR expression is increased in inflammatory cells during developmentof myocardial infarction and in areas of inflammation, such as the atherosclerotic plaque and lymphoid tissuein the lung, but present at low levels in healthy tissue. Further, they demonstrate that genetic deletion orantibody blocking of TILRR function reduces development of disease progression, and suggest that TILRRprovides a novel rational target for site- and signal specific inhibition of inflammatory responses in disease.

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