PublisherInfo		
PublisherName	:	BioMed Central
PublisherLocation	:	London
PublisherImprintName	:	BioMed Central

Keeping innate immunity at bay

ArticleInfo		
ArticleID	:	4544
ArticleDOI	:	10.1186/gb-spotlight-20020731-01
ArticleCitationID	:	spotlight-20020731-01
ArticleSequenceNumber	:	210
ArticleCategory	:	Research news
ArticleFirstPage	:	1
ArticleLastPage	:	2
ArticleHistory	:	RegistrationDate : 2002–7–31 OnlineDate : 2002–7–31
ArticleCopyright	:	BioMed Central Ltd2002
ArticleGrants	:	
ArticleContext	:	130593311

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Toll-like receptors (TLRs) recognize pathogen-associated products, such as components of the bacterial cell wall, and activate macrophages and other innate immune cells through a signaling cascade involving serine/threonine kinases of the IRAK family. Richard Flavell and co-workers from Yale University School of Medicine, New Haven, Connecticut report in 26 July Cell that at least one member of the IRAK family, IRAK-M, is a negative regulator of TLR signaling (*Cell* 2002, **110:**191-202). They suggest IRAK-M controls a balance between the innate immune response and excessive production of cytokines, which can be potentially harmful to the host.

Kobayashi *et al.* show that lack of IRAK-M causes increased production of inflammatory cytokines, including interleukin-6 and tumor-necrosis factor α, and an enhanced inflammatory response in the gut of IRAK-$M^{-/-}$ mice infected with the Gram-negative pathogen *Salmonella typhimurium*. IRAK-$M^{-/-}$macrophages did not develop endotoxin tolerance to the bacterial lipopolysaccharide, a little-understood regulatory mechanism that protects from endotoxic shock. TLR signaling following stimulation of macrophages was enhanced in the absence of IRAK-M, and immunoprecipitations suggested that, in wild-type mice, IRAK-M inhibits the release of activating IRAK kinases from the TLR signaling complex, thereby blocking downstream signaling events.

Kobayashi *et al.* conclude that the negative regulatory function of IRAK-M may be required for preventing endotoxic shock and immunopathologies such as Crohn's and other inflammatory bowel diseases.

References

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