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Augmentation of Human Monocyte Responses to Lipopolysaccharide by the Protein S and Mer/Tyro3 Receptor Tyrosine Kinase Axis

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Abstract

Resolution of the inflammatory response requires coordinated regulation of pro- and anti-inflammatory mediator production, together with clearance of recruited inflammatory cells. Many different receptors have been implicated in phagocytosis of apoptotic cells (efferocytosis), including Mer, a receptor tyrosine kinase that can mediate recognition and subsequent internalization of apoptotic cells. In this manuscript, we examine the expression and function of the Tyro3/Axl/Mer (TAM) family of receptors by human monocytes. We demonstrate that the Mer ligand, protein S, binds to the surface of viable monocytes via phosphatidylserine-dependent and -independent mechanisms. Importantly, we have identified a novel role for receptor tyrosine kinase signaling in the augmentation of monocyte cytokine release in response to LPS. We propose that low-level phosphatidylserine exposure on the plasma membrane of viable monocytes allows protein S binding that leads to TAM-dependent augmentation of proinflammatory cytokine production. Our findings identify a potentially important role for TAM-mediated signaling during the initiation phase of inflammation.

Footnotes

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- The online version of this article contains supplemental material.
- Abbreviations used in this article:

Gas6
growth arrest specific protein 6

GC
glucocorticoid-treated

ΔGla Pros1
Pros1 lacking the Gla domain

MDM
monocyte-derived macrophage

Pros1
protein S

PtdSer
phosphatidylserine

RTK
receptor tyrosine kinase

TAM
Tyro3/Axl/Mer.

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