Abstract

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Molecular mechanism for differential recognition of membrane phosphatidylserine by the immune regulatory receptor Tim4.

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Abstract

Recognition of phosphatidylserine (PS) lipids exposed on the extracellular leaflet of plasma membranes is implicated in both apoptotic cell removal and immune regulation. The PS receptor T cell immunoglobulin and mucin-domain-containing molecule 4 (Tim4) regulates T-cell immunity via phagocytosis of both apoptotic (high PS exposure) and nonapoptotic (intermediate PS exposure) activated T cells. The latter population must be removed at lower efficiency to sensitively control immune tolerance and memory cell population size, but the molecular basis for how Tim4 achieves this sensitivity is unknown. Using a combination of interfacial X-ray scattering, molecular dynamics simulations, and membrane binding assays, we demonstrate how Tim4 recognizes PS in the context of a lipid bilayer. Our data reveal that in addition to the known Ca(2+)-coordinated, single-PS binding pocket, Tim4 has four weaker sites of potential ionic interactions with PS lipids. This organization makes Tim4 sensitive to PS surface concentration in a manner capable of supporting differential recognition on the basis of PS exposure level. The structurally homologous, but functionally distinct, Tim1 and Tim3 are significantly less sensitive to PS surface density, likely reflecting the differences in immunological function between the Tim proteins. These results establish the potential for lipid membrane parameters, such as PS surface density, to play a critical role in facilitating selective recognition of PS-exposing cells. Furthermore, our multidisciplinary approach overcomes the difficulties associated with characterizing dynamic protein/membrane systems to reveal the molecular mechanisms underlying Tim4's recognition properties, and thereby provides an approach capable of providing atomic-level detail to uncover the nuances of protein/membrane interactions.

KEYWORDS: PS recognition; differential membrane recognition

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