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RENAL INJURY

Prevention of talin-1-mediated activation of neutrophils protects against renal ischaemia–reperfusion injury

Integrins are αβ heterodimeric cell-adhesion molecules that support many biological processes, such as neutrophil-mediated tissue injury in inflammatory disorders. New data from Rodger McEver and colleagues show that the large cytoplasmic protein talin-1 is required for integrin activation in renal ischaemia–reperfusion (I/R) injury and neutrophil arrest along vessel walls.

> “...mice expressing talin-1 L325R are protected from renal I/R injury”

Talin-1 activates β3 integrins by binding to membrane-distal and membrane-proximal cytoplasmic regions on the integrin β3 subunit, but its effect in mediating the function of the analogous β2 integrin was previously unclear. Here, the investigators questioned whether talin-1 is required to bind the membrane-proximal site on the integrin β2 subunit to enable neutrophil slow rolling and arrest.

The researchers previously generated knock-in mice that expressed mutated talin-1 (L325R). This talin-1 variant only binds to the distal membrane region on the integrin β subunit. In their recent study, the researchers generated mice that expressed mutant talin-1 only in myeloid cells, such as neutrophils, and used this model to analyse the effects of disrupted talin-1 binding on β2 integrin function, *in vitro* and *in vivo*.

The investigators found that mice expressing talin-1 L325R are protected from renal I/R injury. Their neutrophils exhibited impaired chemokine-induced β2 integrin-mediated arrest, spreading, and migration, but interestingly, selectin-induced β2 integrin-mediated slow rolling was maintained. Neutrophil arrest and spreading, therefore, depended on talin-1 binding to both the distal and proximal membrane regions of the integrin β2 subunit, but binding to the proximal region was not required for the β2 integrin conformational change that facilitates neutrophil slow rolling.

“These data define a requirement for chemokine-induced β2 integrin activation during renal I/R injury, and show that selectin-induced, β2 integrin-mediated neutrophil slow rolling is not sufficient for renal I/R injury or neutrophil migration in response to other inflammatory challenges,” proposes McEver. “These findings are contradictory to previous conclusions that selectin signalling has a dominant role in renal I/R injury.” The researchers now hope to develop new tools to specifically inhibit selectin signalling and distinguish the contributions of selectin-dependent adhesion and signalling *in vitro* and *in vivo*.

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Original article Yago, T. *et al.* Blocking neutrophil integrin activation prevents ischemia–reperfusion injury. *J. Exp. Med.* doi:10.1084/jem.20142358