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Nrf2 and Keap1: A quintessential duet in endothelial cells

Nrf2 is a transcription factor known to modulate blood vessel formation. Various experimental settings, however, attribute to Nrf2 either stimulatory or repressive effects on angiogenesis. Our findings unveil the mechanism of Nrf2-dependent vessel formation, which reaches beyond transactivation of gene expression and reconciles previous discrepancies. We evidence that GDF-15- and SDF-1-induced angiogenesis strongly depends on the presence of Nrf2 protein, but does not rely on its transcriptional activity. Instead, Nrf2 serves as a protein restraining Keap1, its known transcriptional repressor. Angiogenic response is abrogated in Nrf2-deficient endothelial cells but not in cells expressing dominant negative form or Keap1-binding fragment of Nrf2. Deficiency of Nrf2 protein available for Keap1 leads to the overabundance of RhoGAP1, the protein regulating Cdc42 activity. This impairs podosome assembly and disrupts actin rearrangements, thereby preventing angiogenesis. Effects of Nrf2 deficiency can be rescued by concomitant knock down of RhoGAP1 or Keap1. Importantly, in the established murine model of Nrf2 deficiency, the N-terminal fragment of Nrf2 containing Keap1 binding domain is preserved. Thus, this model can be used to characterize Nrf2 as a transcription factor, but not as a Keap1-sequestering protein. Up to date the significance of Nrf2 in cell function has been ascribed solely to regulation of transcription. We demonstrate that Nrf2 serves a protein tethering Keap1 to allow podosome assembly and angiogenesis.