Targeting TGFbeta Bioavailability to Regulate Vascular Stability and Leakage

Nor Eddine SOUNNI1, Leon Van Kempen1, Kerstin Dehne1, Stephen Krane2 and Lisa M. Coussens1

1 Department of Pathology, Cancer Research Institute and Comprehensive Cancer Center, University of California San Francisco, 2340 Sutter Street, N-221, Box 0875, San Francisco, CA, 94115,
2 Department Medicine, Harvard Medical School, 149 13th Street, Charlestown, MA, 02129

ABSTRACT

Significance of ECM as a regulator of vascular function has been hypothesized but not fully investigated. We assessed vessel stability and response to acute tissue stress in vivo in mice where type I collagen metabolism is altered due to presence of a knock-in mutation in the Col1a1 gene, e.g., Colα1(I)rt/r mice. Our data revealed that plasma protein extravasation and vessel leakiness following acute stimulation of skin by topical exposure to mustard oil (MO) or intradermal injection of serotonin, histamine or VEGF–A, in Colα1(I)rt/r mice was attenuated by 50% indicating that vessels resist acute responses due to maintenance of stability. We found that maintenance of vessel stability in Colα1(I)rt/r mice was due to chronic activation of a metalloprotease (MP) in skin since treatment of Colα1(I)rt/r mice with the MP inhibitor GM6001 restored acute vascular responses to mutant animals. We assessed vascular leakage in MMP–2, –8, –13 and –14 deficient mice and found that only in MMP14–deficient mice was vessel stability compromised as evidenced by their increased steady state level of plasma protein leakage. To reveal the molecular pathway being regulated by MMP14, we treated Colα1(I)rt/r mice with neutralizing antibodies to TGFβ or an ALK5 inhibitor and found that vascular responsiveness in Colα1(I)rt/r mice was normalized to characteristic levels as observed in wt mice. The implications of these findings are that pharmacologic manipulation of type I collagen metabolism, MMP14 activity, or TGFβ–induced signaling represents efficacious targets for regulating vascular stability and/or leakiness in vivo.