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Targeting TGFbeta Bioavailability to Regulate Vascular Stability and Leakage

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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., Col$^{\alpha}$1(I)$^{r/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 Col$^{\alpha}$1(I)$^{r/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 Col$^{\alpha}$1(I)$^{r/r}$ mice was due to chronic activation of a metalloprotease (MP) in skin since treatment of Col$^{\alpha}$1(I)$^{r/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 Col$^{\alpha}$1(I)$^{r/r}$ mice with neutralizing antibodies to TGFß or an ALK5 inhibitor and found that vascular responsiveness in Col$^{\alpha}$1(I)$^{r/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 TGFß-induced signaling represents efficacious targets for regulating vascular stability and/or leakiness *in vivo.*