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Coupling of a specific photoreactive triple-helical peptide to crosslinked collagen films restores binding and activation of DDR2 and VWF

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Abstract.

Collagen-based scaffolds may require chemical crosslinking to achieve mechanical properties suitable for tissue engineering. Carbodiimide treatment, often used for this purpose, consumes amino acid sidechains required for receptor recognition, so reducing cell–collagen interaction. Here, we restore recognition and function of both von Willebrand Factor (VWF) and Discoidin Domain Receptor 2 (DDR2) to crosslinked collagen films by derivatization with a specific triple-helical peptide (THP), an approach previously applied to integrin-mediated cellular adhesion. The THP contained the collagen III-derived active sequence, GPRGQOGVNleGFO, conjugated to a photoreactive moiety, diazirine, allowing UV-dependent covalent coupling to collagen films. Crosslinking of collagen films attenuated the binding of recombinant VWF A3 domain and of DDR2 (as the GST and Fc fusions, respectively), and coupling of the specific THP restored their attachment. These derivatized films supported activation of DDR2 expressed in either COS-7 or HEK293 cells, reflected by phosphorylation of tyrosine 740, and VWF-mediated platelet deposition from flowing blood was restored. Further, such films were able to increase low-density lipoprotein uptake in vascular endothelial cells, a marker for endothelial phenotype. Thus, covalent linkage of specific THPs to crosslinked collagen films i) restores their cognate protein binding, ii) triggers the corresponding cellular responses, and iii) demonstrates the broad applicability of the approach to a range of receptors for applications in regenerative medicine.

Graphical Abstract.