Structural basis of the collagen-binding mode of discoidin domain receptor 2

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Discoidin domain receptor 2 (DDR2) is a cell surface receptor tyrosine kinase activated by the fibrillar collagen. DDR2 is expressed in skin, heart, liver, and kidney connective tissue, and is overexpressed in some tumor cells. The direct interaction of collagen with the DS domain in the extracellular portion of DDR2 (DDR2-DS domain) activates its intracellular tyrosine kinase, triggering downstream intracellular signaling cascades that regulate cell proliferation and migration. Little is known about the collagen recognition mode of the DDR2-DS domain at atomic resolution, due to the lack of the three-dimensional structure of the DDR2-DS domain. Here, we have determined the NMR structure of the DDR2-DS domain and the interface on the DS domain for the collagen type II fibril by transferred cross-saturation (TCS) methods. The DDR2-DS domain structure adopts a distorted jellyroll fold, consisting of eight β-strands. The fibril of collagen type II binds to the interloop trench and the surrounding loop region of the DDR2-DS domain. The property of the collagen interface on the DDR2-DS domain has been revealed to contain the combination of charged and hydrophobic residues, as observed for the sequence specific interaction of the α_2 subunit of integrin with collagen. The specific recognition of the collagen by DDR2 is discussed, based on the structural basis of the DDR2–collagen interaction. This study provides a molecular basis for the collagen binding mode of the DDR2-DS domain.