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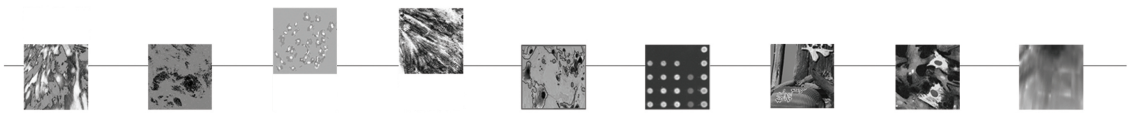


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Prelude to chapters 3 and 4

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Integrins and integrin signaling

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In the heart, cardiomyocytes (CMCs) are surrounded by a mesh of extracellular matrix (ECM). Besides providing structural support to the CMCs, the ECM is also involved in maintaining homeostasis in the healthy heart and in cardiac remodeling following myocardial injury.¹ CMC-ECM interactions are mainly mediated via integrins, which are transmembrane heterodimers consisting of an α - and a β -chain. There are 18 α - and 8 β -subunits that can form 24 different combinations with distinct binding properties.^{2,3} While the extracellular part of integrins bind various components of the ECM, such as fibronectin, laminin and collagen, the intracellular part is connected to the cytoskeleton via talin and α -actinin.⁴ In the heart, integrins are important as mechanotransducers that sense the mechanical forces of the beating heart and consequently induce signaling cascades in the CMC. Since integrins themselves do not possess enzymatic activity, they are linked to other signaling molecules, such as focal adhesion kinase (FAK), Src, integrin-linked kinase (ILK) and p130CAS.^{5,6} The effect of integrin stimulation can be studied *in vitro* by exposing CMCs to soluble integrin receptor ligands containing the Arg-Gly-Asp (RGD) sequence present in fibronectin and other ECM proteins.⁷ One of the effects of integrin stimulation that has been studied using these RGD containing peptides is the release of Ca^{2+} from the sarcoplasmic reticulum (SR). It was shown that integrin signaling led to Ca^{2+} release from the SR via ryanodine receptors.⁸ The release of Ca^{2+} leads to an increase in intracellular Ca^{2+} concentration, which triggers dysferlin-mediated sealing of plasma membrane ruptures caused by the contraction of the heart.⁹ Integrin stimulation has also been shown to induce cardiac hypertrophy.⁶ FAK and Src were shown to be activated upon integrin stimulation, which led to ERK1/2 activation.¹⁰ Furthermore, integrin-linked kinase (ILK) expression is increased in hypertrophic hearts and overexpression of ILK activates prohypertrophic signaling kinases.¹¹ In addition, it was shown that integrin stimulation-induced hypertrophy is nitric oxide-dependent.¹² Although the existing data indicate an important role for integrin signaling in cardiac hypertrophy, the exact pathways through which integrin signaling leads to hypertrophy remain to be clarified.

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