Tissue engineering is a growing area that aims to create, repair, and/or replace tissues and organs by using combinations of cells, scaffolds, biologically active molecules, and physiologic signals. It is an interdisciplinary field that integrates aspects of engineering, chemistry, biology, and medicine. One of the most challenging goals in the field of cardiovascular tissue engineering is the creation of an engineered heart muscle. Unlike heart valves or blood vessels, heart muscle has no replacement alternatives. New discoveries in stem cell biology suggest that stem cells are a potential source of heart muscle cells and blood vessels and can be used to rebuild or replace damaged heart tissue. Recent advances in methods of stem cell isolation, expansion, and culture and the synthesis of new bioactive materials show promise to contribute to the creation of engineered contractile cardiac tissue in vitro and in vivo.

This chapter introduces the basic structural features of myocardium, elucidating the challenges in tissue engineering of a cardiac muscle. It describes the principles of myocardial tissue engineering and reviews various approaches to achieve the ambitious goal of creating contractile heart muscle to treat myocardial infarction and heart failure patients.

The Myocardium

The myocardium is composed mainly of cardiomyocytes, fibroblasts, and the elements of blood vessels: endothelial and smooth muscle cells, macrophages, and extracellular matrix (ECM) (Figure 1.1). Cardiomyocytes constitute only one-third of the total cardiac cell number. However, they occupy more than 70% of cardiac volume. Fibroblasts are the dominant cardiac cell and account for 90% to 95% of nonmyocyte cell mass.

Unlike other somatic tissues, the heart has been viewed as an organ composed of terminally differentiated cardiomyocytes and incapable of regeneration. Recent studies challenge these pre-existing notions regarding cardiac repair/regeneration and suggest that the heart is capable of limited regeneration through the activation and recruitment of a stem/progenitor cell population that is resident in the adult heart.

Cardiomyocytes are tethered in an extensive extracellular network of collagen and other structural proteins, including fibronectins and proteoglycans [Figure 1.2 (see color section)]. The extracellular and intracellular myofibrillar scaffolding is a critical determinant of cardiac shape during normal and abnormal cardiac growth. Collagen is synthesized principally by fibroblasts but also by vascular smooth muscle cells in response to a variety of pathologic stimuli, including increased oxidative and mechanical stress, ischemia, and inflammation.

Of the many collagen types, the major fibrillar collagens are types I (approximately 85%) and III (11%), which constitute the bulk of cardiac ECM. Collagen type I is associated mainly with thick fibers that confer tensile strength and
Heart resistance to stretch and deformation, whereas collagen type III is associated with thin fibers that confer resilience.2

Cardiomyocytes are tethered to the ECM by membrane-spanning proteins called integrins [Figure 1.2 (see color section)]. The extracellular portion of these molecules binds to fibronectins in the ECM. Perimyocyte extracellular proteins such as dystrophin and dystrophin-related proteins contribute to normal cardiogenesis. When altered in abundance, they can produce a cardiomyopathy.6

Myocardial Infarction and Remodeling

Heart failure after myocardial infarction can result from the substantial loss of cardiomyocytes in the infarct zone but more often is precipitated by the delayed and progressive pathologic remodeling of the left ventricle. Cell death in the infarct zone is large in magnitude but short in duration.

When myocardial tissue is injured, normal healing response is initiated through a series of complex events that include acute inflammation, the formation of granulation tissue, and eventual scar formation.7,8 Cytokines and growth factors are released to recruit white blood cells, mainly neutrophils. Monocytes are then called to the wound site where they differentiate into macrophages. The macrophages are responsible for cleaning the infarcted zone and also for recruiting cells such as fibroblasts, endothelial cells, and stem/progenitor cells creating granulation tissue. The formation of blood vessels is essential to the healing of the infarcted myocardium. The granulation tissue is subsequently replaced by an ECM deposited primarily by fibroblasts. The degree of ECM depends on the extent and location (e.g., anterior or apical) of infarction. In most cases, the granulation tissue is remodeled into scar tissue.

Most of the molecules and signal transduction pathways operant in cardiomyocyte growth have a role in hyperplasia of fibroblasts and in the elaboration of collagen. The resultant fibrosis produces altered myocardial stiffness and arrhythmogenesis in ischemic heart disease, cardiac hypertrophy, and congestive heart failure. Collagen synthesis is continuously and variably offset by ECM resorption mediated by matrix metalloproteinases. The activity of these enzymes is increased in ischemic and dilated cardiomyopathy.2 Conversely, the activity of a class of enzymes known as tissue inhibitors of matrix metalloproteinases is reduced in this setting. The resultant excessive collagenolyses may induce myofibrillar slippage and contribute to the dilated thin-walled chamber geometry that characterizes acute and chronic heart failure. This process has been termed left ventricular (LV) remodeling.

Myocardial Regeneration

Myocardial regeneration is an exciting novel therapeutic concept.9 One approach that has received recent attention focuses on repopulation of the injured myocardium by transplantation of healthy cells.10 Several cell types that might replace necrotic tissue and minimize scarring have been considered (Table 1.1). Fetal cardiomyocytes, skeletal myoblasts, and bone marrow stem cells have all shown limited success in restoring damaged tissues and improving cardiac function. Failure to produce new myocardial fibers in clinically relevant numbers was attributed to cell death occurring after engraftment and inability of engrafted myoblasts to differentiate and integrate within the host myocardium; hence, electromechanical coupling is not likely to occur after in vivo myoblast grafting.

An alternative approach includes mobilization of progenitor or stem cells to the damaged