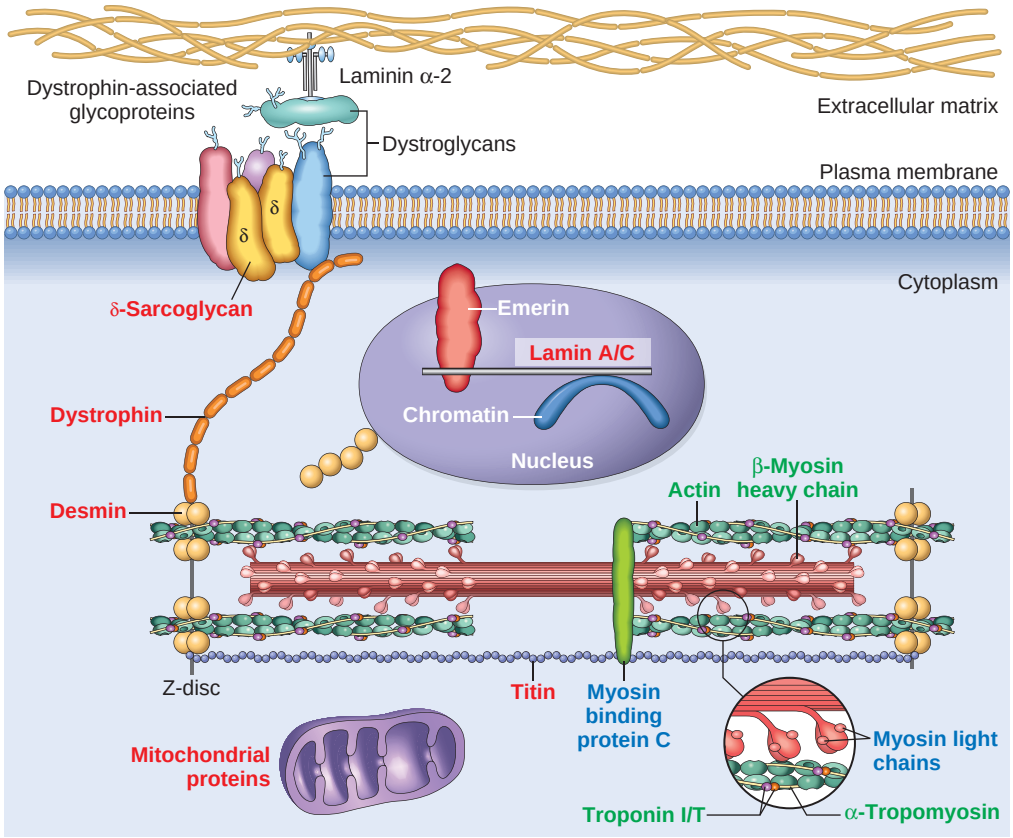

Figure 12-30 Schematic of a myocyte, showing key proteins mutated in dilated cardiomyopathy (red labels), hypertrophic cardiomyopathy (blue labels), or both (green labels). Mutations in titin (the largest known human protein at approximately 30,000 amino acids) account for approximately 20% of all dilated cardiomyopathy. Titin spans the sarcomere and connects the Z and M bands thereby limiting the passive range of motion of the sarcomere as it is stretched. Titin also functions like a molecular spring, with domains that unfold when the protein is stretched and refold when the tension is removed, thereby impacting the passive elasticity of striated muscle.

possibility that ethanol toxicity (Chapter 9) or a secondary nutritional disturbance can underlie myocardial injury. Alcohol or its metabolites (especially acetaldehyde) have a direct toxic effect on the myocardium. Moreover, chronic alcoholism may be associated with thiamine deficiency, which can lead to beriberi heart disease (also indistinguishable from DCM). Nevertheless, no morphologic features serve to distinguish *alcoholic cardiomyopathy* from DCM of other causes.

In other cases, some other toxic insult can progress to eventual myocardial failure. Particularly important is myocardial injury caused by certain chemotherapeutic agents, including doxorubicin (Adriamycin), and even targeted cancer therapeutics (e.g., tyrosine kinase inhibitors). Cobalt is an example of a heavy metal with cardiotoxicity and has caused DCM in the setting of inadvertent tainting (e.g., in beer production).

- *Childbirth.* A special form of DCM, termed *peripartum cardiomyopathy*, can occur late in pregnancy or up to months postpartum. The mechanism underlying this entity is poorly understood but is probably multifactorial. Pregnancy-associated hypertension, volume overload, nutritional deficiency, other metabolic derangements, or an as yet poorly characterized immunological reaction have been proposed as causes. Recent work suggests that the primary defect is a microvascular angiogenic imbalance within the myocardium leading to functional ischemic injury. Thus, peripartum cardiomyopathy can be elicited in mouse models by increased levels of circulating antiangiogenic mediators including vascular endothelial growth factor inhibitors (e.g., sFLT1, as occurs with preeclampsia) or antiangiogenic cleavage products of the hormone prolactin (which rises late in pregnancy). Proangiogenic approaches, including the blockade of prolactin secretion by bromocriptine, represent new therapeutic strategies for treating this disease.
- *Iron overload* in the heart can result from either hereditary hemochromatosis (Chapter 18) or from multiple transfusions. DCM is the most common manifestation of such iron excess, and may be caused by interference with metal-dependent enzyme systems or to injury from iron-mediated production of reactive oxygen species.
- *Supraphysiologic stress* can also result in DCM. This can happen with persistent tachycardia, hyperthyroidism, or even during development, as in the fetuses of insulin-dependent diabetic mothers. *Excess catecholamines*, in particular, may result in multifocal myocardial contraction band necrosis that can eventually progress to DCM. This can happen in individuals with *pheochromocytomas*, tumors that elaborate epinephrine (Chapter 24); use of cocaine or vasopressor agents such as dopamine can have similar consequences. Such "catecholamine effect" also occurs in the setting of intense autonomic stimulation, for example, secondary to intracranial