Dilated cardiomyopathy and structural proteins

D. Fatkin, Molecular Cardiology Division, Victor Chang Cardiac Research Institute, Darlinghurst, NSW 2010, Australia.

Dilated cardiomyopathy (DCM) is a myocardial disorder that is characterised by dilation and contractile dysfunction of the heart chambers, particularly the left ventricle. DCM is common, and is associated with substantial morbidity, including heart failure and arrhythmias, as well as increased mortality. There are numerous potentially treatable causes of DCM, including viral or bacterial infections, drugs, toxins, autoimmune, metabolic, endocrine or nutritional disorders. However, genetic factors are increasingly being recognised to be important causes of DCM. Studies of families in which DCM segregates as a Mendelian trait have been instrumental in studying the genetic basis of DCM and disease-causing mutations in more than 40 genes have been identified. Over the past decade, genetic testing of subsets of the more common disease genes has been commercially available but due to the costs involved and relatively low yield, this has not been routinely incorporated into clinical practice. Recent advances in next-generation sequencing are now enabling known disease genes to be screened more rapidly and efficiently, and are facilitating the discovery of new disease genes. Disease genes identified to date have encoded proteins in the sarcomere, Z-disc, cytoskeleton, sarcolemma and nucleus. Many of these proteins are components of a structural scaffolding that spans from the nucleus to the cell surface and extracellular matrix. Defects of this scaffolding can result in reduced transduction of generated force, altered signaling and reduced resistance to mechanical stress. Examples of commonly-mutated genes in this pathway include the genes encoding lamin A/C (*LMNA*), dystrophin (*DMD*), and desmin (*DES*). Sarcomere protein genes have been shown to cause hypertrophic cardiomyopathy, but many of these same genes have been associated with DCM, including the genes encoding myosin heavy chain (*MYH7*, *MYH6*), cardiac troponin T (*TNNT2*) and cardiac actin (*ACTC1*). It remains unclear why mutations in the same genes can give rise to these different phenotypes. A range of genes encoding cardiac ion channels and ion channel-related proteins (*SCN5A*, *RYR2*, *PLN*), DNA and RNA binding proteins (*PRDM16*, *NKX2-5*, *RBM20*) and other cardiomyocyte components have also been associated with DCM. Most recently, mutations in the *TTN* gene that encodes the giant sarcomeric protein titin, have been shown to be present in approximately 25% patients with familial and sporadic forms of DCM. This is a remarkable discovery that is expected to have a substantial impact on the role of genetic testing in DCM. Titin has major roles in sarcomere and Z-disc stability and signaling. Taken together, current data indicate that perturbation of diverse cardiomyocyte functions can result in myocardial contractile impairment. Whether genetically-determined primary defects converge in one or more common downstream pathways remains to be determined. Insights gained from next-generation sequencing studies of DCM patient cohorts are likely to provide new perspectives on disease pathogenesis and will ideally help to identify novel and more effective approaches to diagnosis, treatment and prevention of DCM.