Abstract.

Rapid impulse propagation is a defining attribute of the pectinated atrial myocardium and His-Purkinje system (HPS) that safeguards against atrial and ventricular arrhythmias, conduction block, and myocardial dyssynchrony. The complex transcriptional circuitry that dictates rapid conduction remains incompletely understood. Here, we demonstrate that ETV1 (ER81)-dependent gene networks dictate the unique electrophysiological characteristics of atrial and His-Purkinje myocytes. Cardiomyocyte-specific deletion of ETV1 results in cardiac conduction abnormalities, decreased expression of rapid conduction genes (*Nkx2–5*, *Gja5*, and *Scn5a*), HPS hypoplasia, and ventricularization of the unique sodium channel properties that define Purkinje and atrial myocytes in the adult heart. Forced expression of ETV1 in postnatal ventricular myocytes (VMs) reveals that ETV1 promotes a HPS gene signature while diminishing ventricular and nodal gene networks. Remarkably, ETV1 induction in human induced pluripotent stem cell-derived cardiomyocytes increases rapid conduction gene expression and inward sodium currents, converting them towards a HPS phenotype. Our data identify a cardiomyocyte-autonomous, ETV1-dependent pathway that is responsible for specification of rapid conduction zones in the heart and demonstrate that ETV1 is sufficient to promote a HPS transcriptional and functional program upon VMs.