protein partners, whereas in fascia AJs, the classical cadherin N-cadherin is primarily anchored to the actin microfilaments of the cytoskeleton and promotes cell–cell adhesion through extracellular associations of its cadherin repeat domains.[268–270] Interestingly, the protein components of desmosomes and fascia AJs are not mutually exclusive.[270,271] In fact, the mechanical junctions of the ID are an admixture of desmosomal and fascia adherens proteins that form a hybrid functional zone, the area composita.[269,272,273] Therefore, even if ARVC has been traditionally considered as a desmosomal disease, it is now reasonable to consider that the mechanistic basis of ARVC may extend beyond the strict functional zone of the desmosome, to that of the area composita. Supporting this concept, pathologic variants in *CTNNA3* (another gene in the area composita), which encodes for αT-catenin, has also been identified in patients with ARVC who were negative for pathologic variants in the main desmosomal genes.[115] α-catenins are natural partners of the cytoplasmic domain of classical cadherins, that is, N- and E-cadherins, and, in the case of N-cadherin, act as its go-between for anchoring to the actin cytoskeleton.

The fact that cadherin-2, like its desmosomal cadherin counterparts, is a major player in the ID is also supported by the *Cdh2* cardiac-specific mouse model with deletion of N-cadherin in the adult mouse heart causing dissolution of the ID structure, including loss of both desmosomes and AJs, demonstrating that desmosome integrity is also cadherin-2 dependent.[274] These mice also exhibited modest, albeit atypical, DCM and spontaneous ventricular arrhythmias that resulted in SCD.[274] This increased arrhythmic propensity (all mice experienced SCD approximately 2 months after deleting N-cadherin from the heart) was probably due to a reduced and heterogeneously distributed connexin-43, causing loss of functional GJs and partial cardiomyocyte uncoupling and highlighting the prominent role of cadherin-2 in all types of functional junctions in the ID.[275] GJ decreases in number and size, with concomitantly increased arrhythmia susceptibility, have also been demonstrated in the context of N-cadherin heterozygous null mice, with 30%–60% of these mice developing VT, suggesting that cadherin-2 haploinsufficiency might create an important arrhythmogenic substrate.[276] ID remodeling with concomitant reduction of localization of desmosomal proteins, connexin-43, and cadherin-2 has also been demonstrated in ventricular tissues of transplanted hearts of patients with ARVC, further supporting the involvement of cadherin-2 in ARVC pathogenesis.[277]

## 4.2. Ion channel defects

Cardiac cells are excitable cells that can generate and propagate an AP, the electrical signal that induces cardiomyocyte contraction. The cardiac AP is generated by ions moving across the cell membrane that, by depolarization, takes the cell from the resting state to an activated state and then, by repolarization, back to the resting membrane potential.[278] All phases of the cardiac AP occur via the synergistic activation and inactivation of several voltage-dependent ion channels. In contractile cardiomyocytes, APs are triggered by the acute entrance of sodium ions ($Na^+$) inside the cell, resulting in an inward current ($I_{Na}$) (*SCN5A*) that shifts the membrane potential from its resting state (−90 mV) to a depolarization state (+20 mV). This phase is followed by the efflux of potassium ($K^+$) ions through an outward current named $I_{to}$, which initiates cell repolarization. This in turn is followed by the plateau phase, a short period of constant membrane potential due to the balance between inward calcium ($Ca^{2+}$) currents ($I_{CaL}$) through the voltage-dependent L-type calcium channels (LTCCs) and time-dependent delayed-rectifier outward $K^+$ currents (mainly slow delayed-rectifier $I_{Ks}$ [KCNQ1] and rapid delayed-rectifier $I_{Kr}$ [KCNH2]). At this point, the $Ca^{2+}$ entry through the LTCC triggers a much larger release of $Ca^{2+}$ from sarcoplasmic reticulum (SR) stores through the ryanodine receptor channel type 2, producing a systolic increase in the intracellular $Ca^{2+}$ needed for cell contraction. Upon LTCC inactivation, the net outward $K^+$ currents repolarize the cell and bring the membrane potential to its resting state. The balance between $Ca^{2+}$ and $K^+$ currents therefore determines the AP duration. The basal and acetylcholine-dependent inwardly rectifying $K^+$ currents ($I_{K1}$ and $I_{KACh}$) control the final repolarization and determine the resting membrane potential. $Ca^{2+}$ is then extruded from the cell through the $Na^+/Ca^{2+}$ exchanger (NCX) type 1 and taken back into the SR through the SR $Ca^{2+}$-ATPase type 2a, thereby restoring low intracellular $Ca^{2+}$ levels, allowing cell relaxation during diastole.

Pacemaker cells are distinct from other cell types in showing automaticity, a property resulting from both voltage-dependent and calcium-dependent mechanisms.[279] The former involves the funny current ($I_f$) carried by hyperpolarization-activated cyclic nucleotide-gated channels,[280] which have several unusual characteristics, such as activation on hyperpolarization, permeability to sodium and potassium ions, modulation by intracellular cyclic adenosine monophosphate, and a small single-channel conductance. The latter involves spontaneous calcium release from the SR,[281] which activates $I_{NCX}$. The crucial role of calcium-dependent mechanisms has been demonstrated in mice with complete atrial-specific knockout of NCX, which has shown no pacemaker activity.[282] Both mechanisms result in spontaneous depolarization responsible for the rising slope of the membrane potential. When the proper ion current flows are disturbed, electrical abnormalities in the form of arrhythmias occur.

### 4.2.1. *SCN5A*

The *SCN5A* gene, which encodes the alpha subunit of the voltage-gated sodium channel $Na_v1.5$, is responsible for the inward sodium current ($I_{Na}$).[283] This current is the main component of rapid depolarization in cardiomyocytes and is responsible for the AP upstroke, which subsequently initiates the multistep excitation–contraction coupling cascade.[284]