Lonely but diverse: Cav1.3 L-type Ca\(^{2+}\) channels in cochlear inner hair cells

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What do cerebellar Purkinje cells, working myocardin, skeletal muscle myocytes and cochlear inner hair cells (IHCs) have in common? Their high-voltage activated (HVA) Ca\(^{2+}\) currents are mediated almost exclusively by a single calcium channel type: Cav2.1 (P-type) in Purkinje cells, Cav1.2 L-type in the heart, Cav1.1 in skeletal muscle and Cav1.3 in IHCs. In most other electrically excitable cells several HVA Ca\(^{2+}\)-channel types coexist. There, individual Ca\(^{2+}\)-channels can only be studied in the presence of complex cocktails of drugs and toxins sparing the channel component of interest.

In cochlear IHCs, 90% of Ca\(^{2+}\)-current is carried by Cav1.3 channels,\(^1\) one of four known L-type Ca\(^{2+}\)-channels (LTCCs). IHCs are the only cells known so far to express essentially pure Cav1.3 currents. About 80 of these channels\(^2\) are clustered at presynaptic specializations, the synaptic ribbons (20–30 per IHC) which tether synaptic vesicles. Cav1.3 Ca\(^{2+}\)-influx is tightly coupled to synaptic vesicle release.\(^3\) IHCs activate channels not by discrete action potentials, but rather by graded changes in membrane potentials, with louder sounds triggering more positive receptor potentials. The Cav1.3-mediated Ca\(^{2+}\)-signal must quickly follow the sound-induced changes in receptor potentials to ensure precise temporal processing.\(^4\) Receptor potentials occur between around −70 and −20 mV.\(^5\) Structural features encoded within the pore-forming Cav1.3 α1-subunits enable activation even within the negative end of this operating range. This is a unique property absent in other LTCCs or the Cav2 family members (Cav2.1–Cav2.3), the presynaptic Ca\(^{2+}\) channels in neurons.\(^5\)

Cav1.3 being the lonely IHC Ca\(^{2+}\)-channel facilitated studies on their function in the cochlea. This includes the correlation of its functional properties with the dynamics of vesicle release, synaptic transmission and phase-locked firing of afferent neurons,\(^6\) revealing its role for postnatal cochlear development\(^1\) and visualizing the morphology of IHC Cav1.3 clusters along the tonotopic axis.\(^7\) However, more recent studies, including the elegant work by Amy Lee and colleagues published in this issue of Channels,\(^8\) point to a functionally relevant heterogeneity among these channels. They report significant differences in whole-cell Cav1.3 current properties between immature and mature IHCs. In immature IHCs, Cav1.3 channels sustain spontaneous Ca\(^{2+}\)-dependent action potentials driving pre-hearing afferent synaptic transmission important for proper auditory pathway development.\(^2,8\) Immature Cav1.3 channels gave rise to larger currents, activated at more negative voltages, exhibited less Ca\(^{2+}\)-dependent inactivation (CDI) and activated more slowly than their mature counterparts. Although some of these observations confirm and some contradict previous studies in other species, they clearly demonstrate that Cav1.3 channels undergo functional adaptations during development that allow them to adjust gating to their distinct roles during development (pacemaking vs. fast sensory transduction). Further evidence for Cav1.3 heterogeneity emerged from recent work by Tobias Moser's group. They quantitated presynaptic Ca\(^{2+}\)-signals from ribbon-associated Ca\(^{2+}\)-channels using high resolution fluorescence microscopy and detected substantial differences for both size and half maximal activation voltage among ribbon synapses even within an individual hair cell.\(^9\) The fact that only Cav1.3 channels underlie the vast majority of these Ca\(^{2+}\)-signals implies the existence of substantial functional heterogeneity within them.

At present we can only speculate about the molecular mechanisms responsible for this functional diversity and many of them were outlined by Inagaki and Lee.\(^6\) Possibilities range from differential interaction with (modulatory) presynaptic proteins\(^5,8\) to differences in alternative a1-subunit splicing,\(^5,8\) post-translational modification and subunit composition (e.g., association with different β-subunit splice-variants or isoforms).

Inagaki and Lee also confirm another puzzling observation. About half of the Cav1.3 current in IHCs does not inactivate after several seconds of strong depolarizations. One explanation for this is moderation of calmodulin-dependent CDI by competing Ca\(^{2+}\)-binding proteins.\(^6\) But another important factor is very slow voltage-dependent inactivation (VDI), which becomes the limiting factor for inactivation rate when CDI is small. This very slow VDI is not observed with heterologously expressed Cav1.3 channels\(^8\) or in Cav1.3 current components in sinoatrial node cells.\(^7\) Yet, it is functionally relevant because it supports continuous channel availability also during prolonged strong sound stimuli. The molecular mechanism for this IHC-specific property is also still unknown.

Although Cav1.3 channels are the lonely contributors to IHC Ca\(^{2+}\) currents the Why and the How of their functional diversity still leaves room for further studies. The paper by Amy Lee’s group is a valuable contribution to understanding how the fine-tuning of these channels optimizes cochlear function in mice and humans.

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