Taking ion channel degradation to heart

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Received 30 January 2007; accepted 5 February 2007
Available online 12 February 2007

See article by Jespersen et al. [5] (pages 64–74) in this issue.

A balance between synthesis and degradation of cellular proteins is of natural importance to regulation of protein levels and necessary to retain viability of living cells. Protein degradation often occurs via targeting through ubiquitination and subsequent decomposition in the cellular proteasome [1]. Some other pathways may either not utilize ubiquitination or degrade proteins via lysosomal catalysis. Ligation of proteins to ubiquitin (a small reusable 8.5-kDa protein) requires a sequential three-step action of specific enzymes (termed E1 to E3). Through this process a C-terminal glycine residue of ubiquitin is activated in an energy (i.e. ATP)-requiring step by an activating enzyme (E1) binding ubiquitin to a cysteine residue of E1. Ubiquitin is then transferred to a cysteine residue of an ubiquitin-carrier protein, E2. In the third step, catalysed by ubiquitin-protein ligases (E3), ubiquitin is linked by its C-terminus to an ε-amino group of the substrate protein’s lysine residues [2].

Several families of E3 enzymes exist and confer specificity to protein degradation procedures. Among ubiquitin-protein ligases the “neural precursor cell-expressed, developmentally down-regulated isoform 4-2” (NEDD4-2) is not an unknown one. It is a member of the C2-WW-HECT (WW is “tryptophane–tryptophane” and HECT is “homologous to the E6-accessory protein”) type E3 ubiquitin ligases, and previous work has established a physiologically relevant involvement in the regulation of a number of membrane proteins, including receptors and ion transporters. Sodium channels such as cardiac NaV1.5 subunits, amiloride-sensitive epithelial sodium channels (ENaC), and neuronal sodium channels are ubiquitinated through NEDD4-2 and subsequently degraded [3]. E3 ligases of the HECT family contain WW binding sites which are crucial for interaction with the proline-rich binding sequence of the target proteins (XPPXY or PY motifs).

Delayed rectifier currents are important in regulation of cardiac repolarization, and associated disorders are causative for a variety of arrhythmias. While previous work mainly focused on functional short-term regulation of KCNQ1 channels and resultant native IKs – for instance by neurohumoral factors or biophysical consequences of β-subunit interactions – recent attention has been drawn to longer-term arrhythmia remodeling with respect to gene-expression in different cardiac disease entities (e.g. [4]). Ongoing research is working on unravelling regulatory mechanisms of ion channel gene transcription and protein synthesis.

In this issue of Cardiovascular Research, Jespersen et al. take the analysis of slow cardiac delayed rectifier physiology to another level and provide novel incentives for future research [5]. With their present study these investigators elegantly demonstrate that NEDD4-2 and other members of this E3 ubiquitin-ligase family work on degrading KCNQ1 protein. Their study utilizes a diverse array of experimental procedures and an integrative concept to bring the molecular study of protein–protein interactions into perspective with its native cellular electrophysiological consequences. The authors show that NEDD4-2 reduces the amount of KCNQ1 protein in eukaryotic cells with subsequent reduction in ionic current levels. They provide evidence for a direct interaction of the KCNQ1 C-terminus with E3 ligases and succeed in demonstrating functional specificity by use of a catalytically inactive NEDD4-2 mutant as well as mutation of the target PY motif in KCNQ1. Other ion channels may be degraded along a similar pathway, but the rapid delayed rectifier current (IKr) and its underlying subunit KCNH2 appear to not be a target for these ligases [6]. While this evidence suggests specificity it cannot finally be proven within the present work. It would be interesting to further address this issue by using a knock-down...
approach for NEDD4-2 to study consequences for cardiac electrophysiology.

How do the results of the present report potentially relate to human disease? Among prominent examples for a role of protein degradation in cardiovascular pathology is the cellular basis of Liddle’s syndrome, a rare hereditary monogenic form of arterial hypertension. This entity is caused by mutations within the PY motif of ENaC [7]. The mutated PY motif causes reduced ENaC ubiquitination, and subsequent channel hyperactivation leads to increased fluid absorption and arterial hypertension.

While the ubiquitination pathway may be naturally important to degradation of malprocessed ion channel proteins, dysregulation of enzymes themselves could potentially be involved in disease mechanisms. At this point it is worth mentioning that nowadays about 30% of patients with clinical long QT syndrome are still unclassified. Taking the authors’ conclusions further, one is tempted to speculate that alterations in synthesis or degradation of cardiac ion channel subunits may potentially provide novel clues to cardiac electrical pathology. Further work should address protein degradation in states associated with altered IKs function such as familial atrial fibrillation, heart failure, and congenital as well as acquired long QT syndromes. If altered NEDD4-2 activity leads to more or less IKs, a potential therapeutic tool could be at hand (e.g. proteasome inhibitors like bortezomib).

Along these lines we still have to learn more about the rise and fall of each specific cardiac ion channel subunit with respect to deciphering individual synthesis and degradation pathways.

Acknowledgement

Funding from the Deutsche Forschungsgemeinschaft (EH 201/2-1) is gratefully acknowledged.

References