Shifting Paradigms in Gap Junction Turnover

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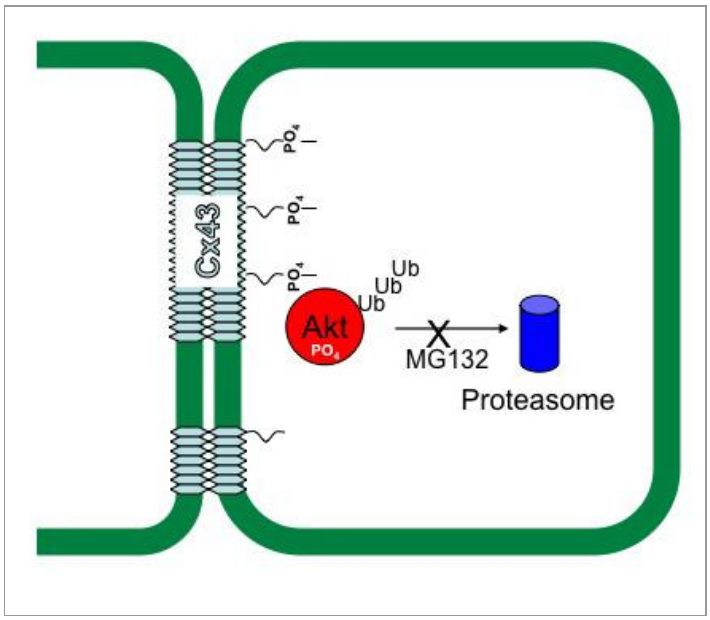
Most cells communicate directly with their neighboring cells through gap junctions, where channels in closely apposed membranes facilitate the exchange of small molecules such as ions and metabolites. These channels are comprised of one or more type of integral membrane protein from the connexin gene family, with connexin 43 (Cx43) being the most ubiquitous. Loss of function mutations in this and other connexin proteins have been associated with human disease, as gap junctions play essential roles in development, tissue homeostasis, cell growth, and the coordination of electric signals between nerve, heart muscle, and smooth muscle cells of the intestine. For reasons that are not completely understood, connexins have remarkably high turnover rates. Previous investigations into the mechanisms that govern Cx43 degradation have demonstrated that proteosomal inhibitors stabilized Cx43 in gap junctions, leading to larger junctions. This observation was thought to be caused by the inhibition of turnover of ubiquitinated Cx43. However, newly published results from a study led by postdoctoral fellow Dr. Clarence Dunn and member Dr. Paul Lampe from the Human Biology and Public Health Sciences divisions have turned this picture on its head.

Dunn *et al.* demonstrated that when all the amino acids required for ubiquitination of Cx43 are replaced, the altered Cx43 protein behaves like wild-type Cx43. This led them to suspect that another protein was being ubiquitinated which controls the rapid turnover of Cx43. In particular, Dunn *et al.* hypothesized that the protein Akt may be regulating Cx43 turnover at gap junctions. Their reasoning is based on observations that Akt relocates to the plasma membrane upon ubiquitination and that Akt has been shown to phosphorylate Cx43. In the present study, the authors found that when Akt activity is blocked through chemical inhibition or with a dominant negative variant of Akt that prevents wild-type Akt from functioning, Cx43 phosphorylation and localization at gap junctions is reduced. They also show that when Akt is ubiquitinated, Cx43 is a target of Akt-specific phosphorylation and the gap junctions become larger. They speculate that phosphorylation regulates Cx43 incorporation into gap junctions. Although the authors recognize that multiple signaling pathways can signal for gap junction turnover, their contribution corrects the long-standing misconception that Cx43 turnover is initiated by ubiquitination of Cx43. This finding will hopefully lead investigations on the mechanics of connexin function in the right direction.

Dunn CA, Su V, Lau AF, Lampe PD. 2011. Activation of AKT, but not connexin43 ubiquitination, regulates gap junction stability.*The Journal of Biological Chemistry*, Epub ahead of print, doi: 10.1074/jbc.M111.276261



Clarence Dunn, with modifications by EM Scherer

An updated model of connexin 43 (Cx43) turnover explains how proteasomal inhibition leads to larger gap junctions: MG132 inhibits proteasomal degradation of ubiquitinated (Ub) Akt. Ubiquitinated Akt is phosphorylated/activated. Activated Akt phosphorylates Cx43. Phosphorylated Cx43 relocates to the plasma membrane, stabilizing junctions, reducing junction turnover and enlarging junctions.