Do CAR and CAR family members aid in gap junction formation?

Gap junctions consist of an array of densely packed transmembrane channels that provide direct cell-to-cell communication. Gap junctions are widely distributed and contribute to multiple functions of cells from coordinating heartbeat, to insulin secretion, to neurological functions. Their importance for the coordination of multi-cellular live is supported by the large number of existing connexins (the gap junction proteins) with 21 different members expressed in humans alone. Connexin43 is the most widely distributed and best studied connexin protein. Gap junction channels consist of two half or hemi-channels (termed connexons), each provided by one of two neighboring cells that dock head-on to form the complete, two plasma membranes spanning gap junction channel. While we know well how gap junctions form, the field still struggles to explain how and where the first connexons dock. Apparently, some helper proteins are necessary. As gap junctions have been found in the vicinity of tight and adherens junctions, one concept postulates that these junctions reduce the nominal distance of plasma membranes, and thus allow connexons to interact and dock. In article 2000031 of this issue, Fritz Rathjen presents novel and exciting evidence suggesting that CAR and CAR-family members (BT-IgSF, CLMP, ESAM) regulate gap junction function and indeed may aid in connexon docking.\(^{[1]}\) CAR stands for Coxsackie and Adenovirus Receptor, transmembrane proteins of the Ig-like cell adhesion protein superfamily that provide cell-cell adhesion via homophilic binding. They received their name as coxackie, and adenoviruses use the protein as a receptor and to somehow move directly from cell to cell.\(^{[2]}\)

We know that a plethora of proteins including the scaffolding protein ZO-1 (zonula occludens-1 which binds to most connexins via its PDZ-2 domain), phosphatases, kinases, ubiquitinases and cytoskeletal proteins (drebrin/actin, microtubules) interact with connexins during all stages of the gap junction live cycle from biosynthesis, to functional regulation, to endocytosis and degradation\(^{[5,6]}\); however no experimentation has provided conclusive evidence that would pinpoint a protein or mechanism to connexon docking. Thus, it is tempting to speculate that ZO-1 could interact with CAR (via its PDZ-domain 1) and connexin proteins (via its PDZ domain 2) to facilitate connexon docking. Future research should reveal whether CAR and CAR family members represent the long searched after proteins that allow initial gap junction connexons to dock, or what other role they might play in gap junction regulation. No matter what role CAR and CAR family members play in gap junction function, it ought to be explored.

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