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# *C. elegans* PAQR-2
## A Regulator of Membrane Homeostasis

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## ABSTRACT

The progestin and adipoQ receptor (PAQR) protein family is characterized by a 7-transmembrane domain, and a topology reversed that of G-protein coupled receptors, i.e. the N-terminus resides in the cytoplasm. Despite the presence of this class of receptors in humans, as well as in the established model organisms, the intracellular signaling pathway has not been adequately elucidated. The most extensively researched PAQR proteins are the mammalian adiponectin receptors, ADIPOR1/2, which mediate the insulin-sensitizing actions of adiponectin on glucose uptake, fatty acid oxidation and gluconeogenesis. AMPK and PPARα are downstream targets of the ADIPORs, and ceramide signaling has also been implicated in mice and yeast. The aim of our studies of the PAQR protein family in *C. elegans* is to further elucidate their downstream signaling pathway using a model organism well suited for the generation of unbiased knowledge through forward genetics screens.

We have focused our research on the *C. elegans* loss of function mutant of *paqr-2*. This protein is closely related to the mammalian ADIPORs and the mutant displays several interesting phenotypes. A forward genetics screen led us to identify IGLR-2 as a protein that physically interacts with PAQR-2 on cell membranes. The *paqr-2* and *iglr-2* mutants display identical phenotypes: sensitivity to cold and exogenous glucose as well as a withered tail tip morphology defect. All three phenotypes can be suppressed by mutations that directly or indirectly increase expression of Δ9 desaturases, enzymes that convert saturated fatty acids (SFA) into unsaturated fatty acids; conversely, *paqr-2* and *iglr-2* mutants have increased levels of SFA and decreased expression of the Δ9 desaturase reporter *pfat-7::GFP*. Poikilotherm organisms, such as *C. elegans,* adapt to a decreased environmental temperature in part by adjusting the fluidity of their cellular membranes. We hypothesized that PAQR-2 and IGLR-2 may act as regulators of membrane fluidity, and measured this property using fluorescence recovery after photobleaching, FRAP. The results reveal that *paqr-2* and *iglr-2*, unlike wild type, do have reduced membrane fluidity upon challenge with low temperature or glucose supplementation, and that this defect can be suppressed by mutations know to promote Δ9 desaturase activity or rescued by detergents provided at membrane-fluidizing concentrations.

We conclude that the adiponectin receptor homolog PAQR-2, and its partner IGLR-2, are involved in the *C. elegans* homeoviscous adaptation response and regulate membrane fluidity through activation of Δ9 desaturases.

**Keywords:** PAQR, LRRIG, glucose, membrane fluidity, desaturase, homeoviscous adaptation