INSTITUTIONEN FÖR KEMI OCH MOLEKYLÄRBIOLOGI

Membrane Fluidity Regulation:
From *C. elegans* to mammalian cells

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ABSTRACT

Biological membranes are primarily an assembly of lipids and proteins. Collectively, these constituents within a phospholipid bilayer determine the physical membrane properties such as fluidity, viscosity, thickness, packing and permeability. Maintenance of membrane properties within acceptable margins, i.e. membrane homeostasis, is fundamentally important for cellular processes. For example, it is a well-established phenomenon that poikilothermic organisms, that cannot control their body temperature, constantly adapt their membrane lipid composition in order to maintain optimal membrane fluidity for membrane functions in spite of variation in ambient temperatures. Regulatory mechanisms must also exist in mammals to maintain membrane lipid heterogeneity across the secretory pathway and to compensate for dietary lipid variation. However, the molecular mechanisms of such an adaptive response in mammals remain poorly understood. Here, using systematic genetics, lipidomics and membrane property assays, we have established that the PAQR-2/IGLR-2 complex in *C. elegans* and AdipoR2 (a PAQR-2 homolog) in mammalian cells specifically respond to the toxic membrane-rigidifying effects of dietary saturated fatty acids (SFAs) and promote fatty acid desaturation to restore membrane composition and fluidity.

In an attempt to understand other mechanisms essential to prevent SFA-mediated cellular toxicity, we also performed an unbiased forward genetic screen in *C. elegans.* Strikingly, this screen for SFA-tolerance genes led only to the isolation of novel *paqr-2* and *iglr-2* alleles; this strongly indicates that *paqr-2* and *iglr-2* are important genes specifically essential to respond to toxic effects of dietary saturated fats. In particular, we noted that in worms and cells that lack PAQR-2/AdipoR2 function, exogenous SFAs becomes rapidly incorporated into membrane phospholipids, leading to membrane rigidification. This was accompanied by an abnormal transcriptional response, impaired mitochondrial respiration and increased ER-UPR as measured in HEK293 cells. Interestingly, we noticed that the toxic effects of exogenous SFAs can be completely mitigated by supplying the cultured cells with small amounts of membrane fluidizing unsaturated fatty acids (UFAs). Consistently, we also found that facilitating the accumulation of UFAs either with mutations in *fld-1* in worms or silencing the *fld-1* mammalian homologs TLCD1/2, which normally function to limit the incorporation of polyunsaturated fatty acids in membrane phospholipids, is protective and able to attenuate SFA-mediated cellular toxicity. Altogether, these results suggest that maintenance of an optimal SFA/UFA ratio is crucial for normal cellular function and that the PAQR-2/AdipoR2 proteins essentially act as "**guardians of membrane homeostasis**".

Keywords: PAQR-2, adiponectin receptors, IGLR-2, saturated fats, membrane fluidity, fatty acid desaturation, unsaturated fatty acid, membrane homeostasis