Lipid antagonists regulate protein clustering

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Abstract
I hypothesize that protein clustering is regulated by specific lipids that block direct or indirect protein interactions. This suggests a therapeutic strategy where selective lipid intake or altering lipid metabolism creates cell type-specific membrane zones that can be individually targeted.

Keywords
proteolipid code, lipid antagonist, lipid fingerprint, lipid glue, zone

Background
The proteolipid code is an interactome and theoretical framework centred around membrane zones[1]. Zones include proteins associated with lipid fingerprints[2], protein isles, and voids with no protein. The specificity of proteins for lipids creates fingerprints, while the amalgamation of protein-fingerprint units creates isles as well as voids with leftover lipids. Any of these zones can be recognized by peripheral proteins or other molecules such as nucleic acids or drugs. Here I hypothesize that specific lipids compete for fingerprint sites to prevent aberrant or homeostatic protein clustering.

Concept
Antagonistic lipids could block protein interactions that are either direct or through lipid glue, which intercalates between proteins to stabilize complexes[3-11] (Figure 1). They could also influence protein conformation to affect clustering. Most or all membrane lipids can be assigned antagonistic ability, as bulk lipid removal aggregates proteins. This is especially true for copies of the same protein which have a propensity for self-clustering due to their identical hydrophobic domains. It is possible that cells synthesize a great variety of lipids to prevent protein clustering among other things.

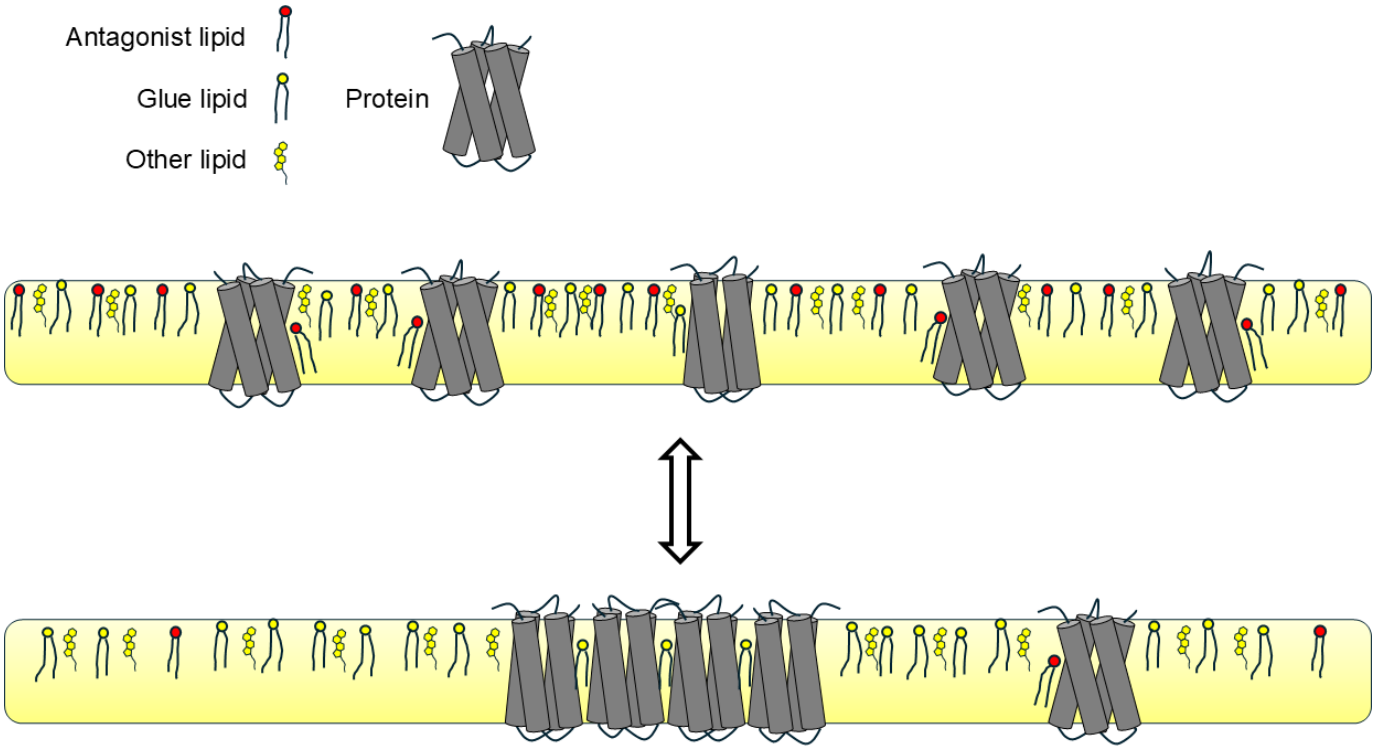

Figure 1. Hypothetical scenario where lipids regulate protein clustering.

Evidence

Reducing lipid complexity tends to cause protein aggregation in molecular simulations[12-14]. Anionic lipids and hydrophobic mismatch are often potent factors, and branched islands are common. Replacement of cardiolipin with monolysocardiolipin in the lipid fingerprints of mitochondrial respiratory complexes[9] may inhibit their assembly into supercomplexes and be responsible for Barth syndrome. Cholesterol-mediated clustering of T cell receptors can be disrupted with cholesterol sulfate[15,16]. The ganglioside GM3 inhibits insulin and epidermal growth factor receptors by preventing their homo- or hetero-oligomerization[17-20]. These examples demonstrate that protein clustering is encoded by a complex lipidome.

Opportunities

This discussion suggests that cell surface zonation can be selectively controlled by altering lipid metabolism or intake through drugs, supplements, or specialized dieting. Nuances between cell types could therefore be exaggerated and their individual responses selectively targeted. It has been noticed that upregulation of endogenous lipid synthesis and lower reliance on extracellular lipids is a hallmark, and perhaps a cardinal weakness, of cancer[21]. An improved knowledge of lipid antagonism could spur the development of a new generation of magic bullets.

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