Detergents Reimagined: A Clearer Window into Membrane Protein Understanding

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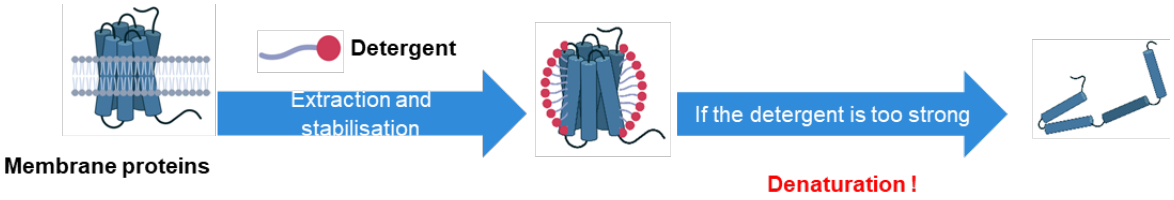
Elucidating the structure of membrane proteins is a major challenge today. Indeed, membrane proteins represent over 60% of therapeutic targets, but only 2.5% of their structures are known.[1, 2, 3] To study membrane proteins, they must first be extracted from the membrane. This is made possible by detergents, which are amphiphilic compounds, meaning that they have a hydrophilic head and a hydrophobic tail. The detergents insert themselves into the lipid bilayer, destabilizing it until it becomes saturated and disintegrates, then forming micelles around the proteins, enabling them to be isolated, stabilized, and characterized.[4]

Nevertheless, many common detergents lead to protein deactivation and denaturation and are therefore not suitable for protein stabilization. The instability of proteins in micelles can be explained by three properties: the flexibility of the alkyl chain; the low resemblance of detergents to the membrane; and unfavorable interactions between detergents and proteins (delipidation in particular) and/or the formation of large detergent-protein complexes.



It is therefore necessary today to synthesize new, milder detergents, enabling good solubilization of these membrane proteins without leading to denaturation. One way of reducing the flexibility of alkyl chains while preserving their hydrophobicity is to incorporate a ring into them, which will also reduce the size of detergent-protein complexes. What we suggest is to synthesize detergents inspired by oxylipins, to which will be grafted a polar head composed of sugars, whose anomeric bond stereochemistry will be β. After synthesis of these detergents, it will be necessary to characterize their physicochemical (hydrophilic-lipophilic balance, critical micellar concentration and micelle shape, size dispersity) and biochemical (protein solubilization, assessing protein stability and activity, and protein purification) properties.

References

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