COMPUTATIONAL INVESTIGATION OF CLD-4 AND PALMITOYLATION

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When Palmitoylated, Membrane Protein Claudin-4 favors to be surrounded by Saturated Lipids (DPPC)

Background

Claudin-4

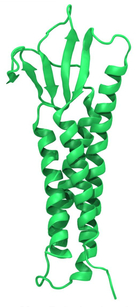
Regulates the paracellular permeability of the membrane
In humans, the claudin family consists of 27 members, each exhibiting complex tissue-specific pattern of expression

Palmitoylation

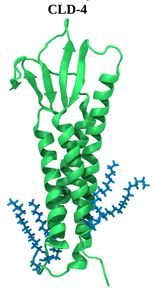
Palmitoylation is a post translational modification of the addition of palmitate and other long fatty acid chains to proteins such as claudin-4 at the cysteine residue

Objectives

How does palmitoylation affect the location and interactions with other lipids of CLD-4 in the transmembrane?



Non-Palmitoylated CLD-4



Palmitoylated CLD-4

Method

Molecular Dynamics

Computational approach using simulations to calculate the trajectories of particles in a system. Systems simulated consisted of coarse-grain and atomistic approaches

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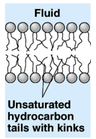
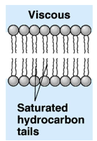
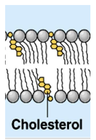
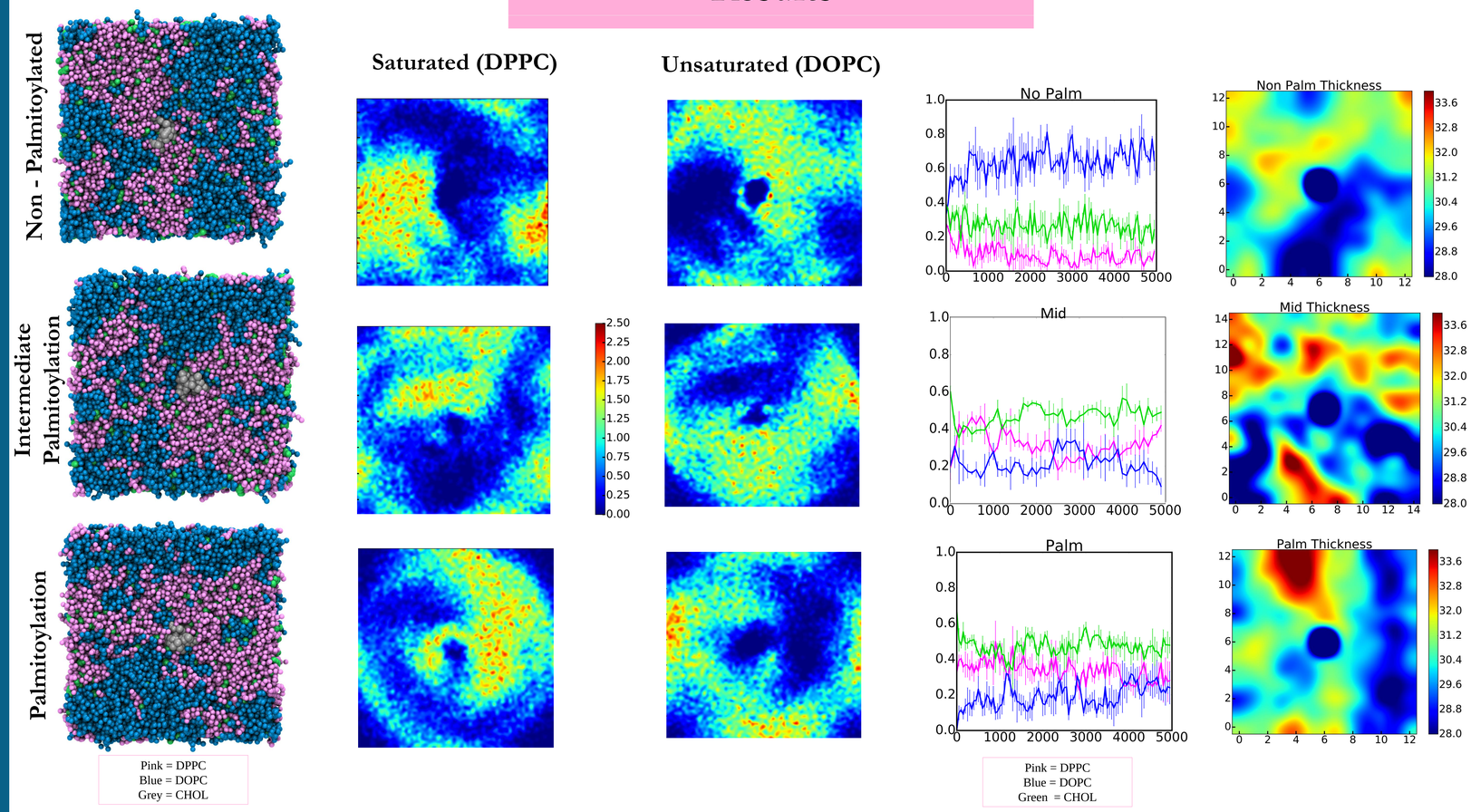
- CLD-4 was places into a transmembrane consisting of saturated lipids (DPPC), unsaturated lipids (DOPC), and cholesterol (CHOL).
  - 2:2:1 ratio respectively
- The transmembrane contained water and 0.15 mol NaCl as well
- 3 experiments with multiple repetitions:
  - 1st system: np-cld4, lipids, water, ions
  - 2nd system: p-cld4, lipids, water, ions
  - 3rd system: mid-cld4, lipids, water, ions





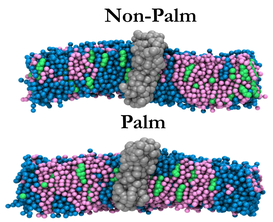


Results



Conclusions

- When palmitoylated, claudin-4 favors to be surrounded by saturated lipids (DPPC)
  - Other claudins with different number of palmitoyl chains also exhibit the same behavior
- Claudin-4 dimers position themselves around DPPC than DOPC
  - Cis interactions



Acknowledgments

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