Claudin 19 and the Effects of Palmitoylation

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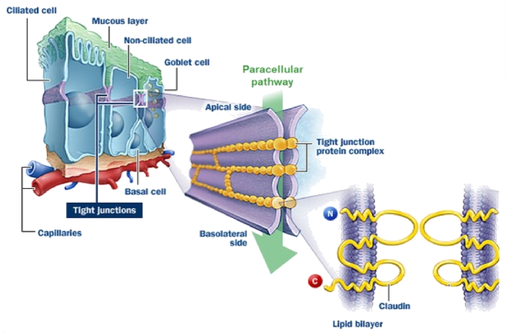
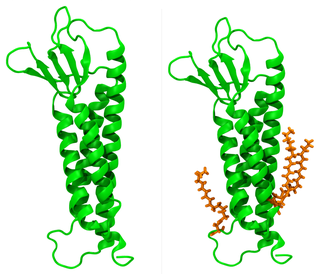
Introduction

- **Claudins**
  - Transmembrane proteins that are an integral components of **tight junctions**.
    - Tight junctions are a **charge and size** selective barriers that regulate paracellular transport.
- **Claudin-19**
  - One of 27 Claudins found primarily in the **kidneys**.
    - Closely associated with diseases related to abnormalities in the reabsorption or lack thereof of magnesium and calcium in the body.
- **Palmitoylation**
  - Is a **reversible lipid modification** in which fatty acids are attached to a cysteine.
    - Claudin-19 has **3** palmitoyl chains attached to **Cysteines-104,183,184**

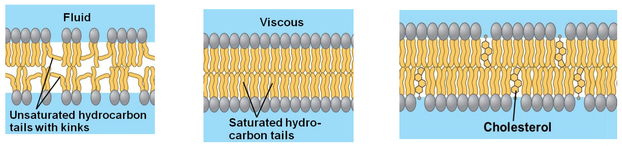




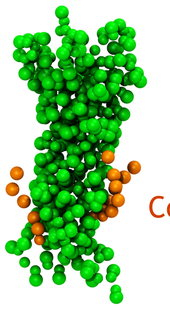
Non-Palmitoylated Palmitoylated

Method

- **Molecular Dynamics**
  - All versions of the protein were **coarse grained** from their atomistic structures.
  - Protein inserted into lipid membrane containing 0.15 M NaCl, and a 2:2:1 ratio of **DOPC**, **DPPC**, and **CHOL** respectively in a periotic boundary condition.

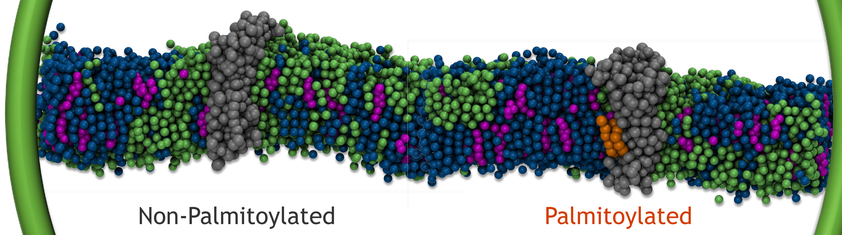


- Simulated in **triplicates** for all systems (Non-Palmitoylated, intermediate, Palmitoylated) for **10μs**.
- Simulations were performed at fixed Temperature (**T =298 K**) and Pressure (**P= 1.01 bar**)



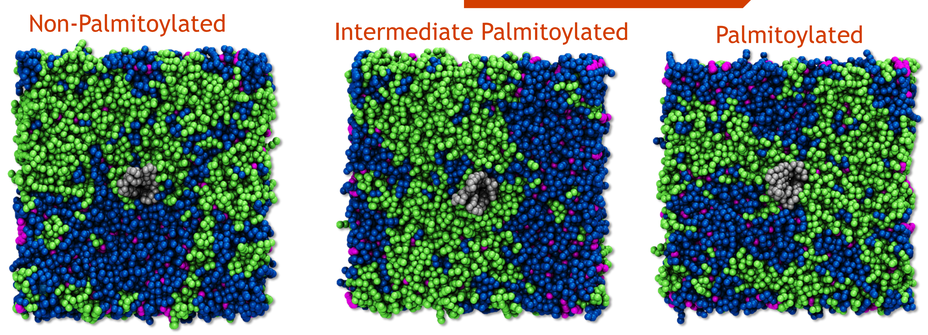
Coarse Grained Claudin-19

Palmitoylation affects Claudin-19 protein's lipid adaptation



Non-Palmitoylated Palmitoylated

Simulations



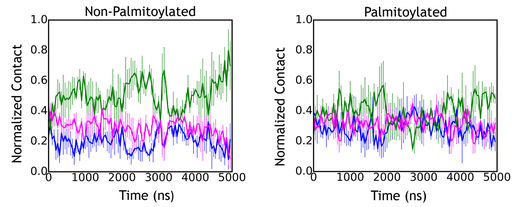
Unsaturated Lipid (DOPC)
Saturated Lipid (DPPC)
Cholesterol (CHOL)
Protein (Claudin-19)

Top view representation of the three systems confined in the periodic boundary condition. Shows that when palmitoyl chains were added there was more contact between the protein and saturated lipids.

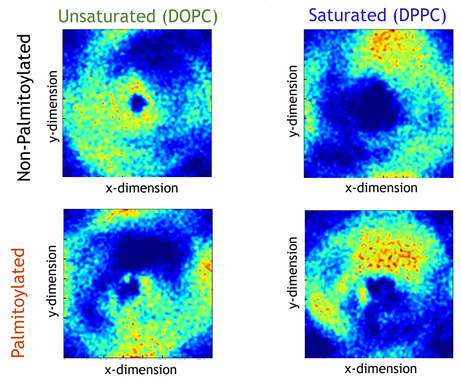
Results

Lipid Mixing Around the Protein

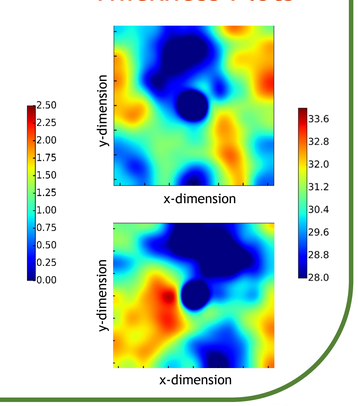
Unsaturated Lipid (DOPC)
Saturated Lipid (DPPC)
Cholesterol (CHOL)
Protein (Claudin-19)



Density Plots



Thickness Plots



Conclusions

- One or more Palmitoyl chains attached to a protein changes the protein's lipid adaptation.
- Palmitoylated protein localizes with the saturated lipids.
- Cholesterol tends localizes with the saturated lipid domain.
- Saturated lipid domains have higher hydrophobic thickness than the unsaturated lipid domains.

Acknowledgements

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