The Effects of Post Translational Modification on Claudin-7 Within the Cell Membrane

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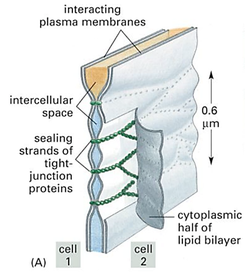
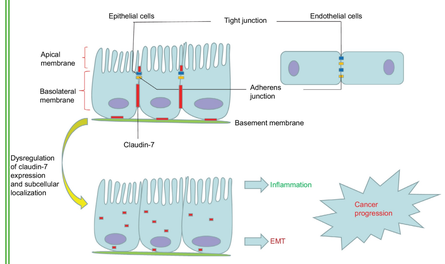
Introduction

Claudins are tight junction proteins that hold two adjacent cells together and regulate permeability

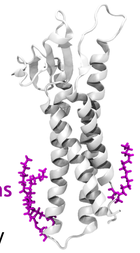


Claudin-7 is a member of the claudin family found in the human body.



Low expression of Claudin-7 protein has been linked to the spread of abnormal breast and colorectal cells.

Proteins undergo posttranslational modification where its juxtamembrane cysteine residues undergo palmitoylation.

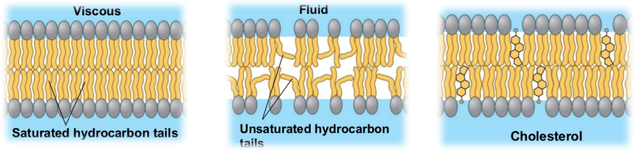


Palmitoylation is the attachment of a saturated fatty acid chain to a protein.

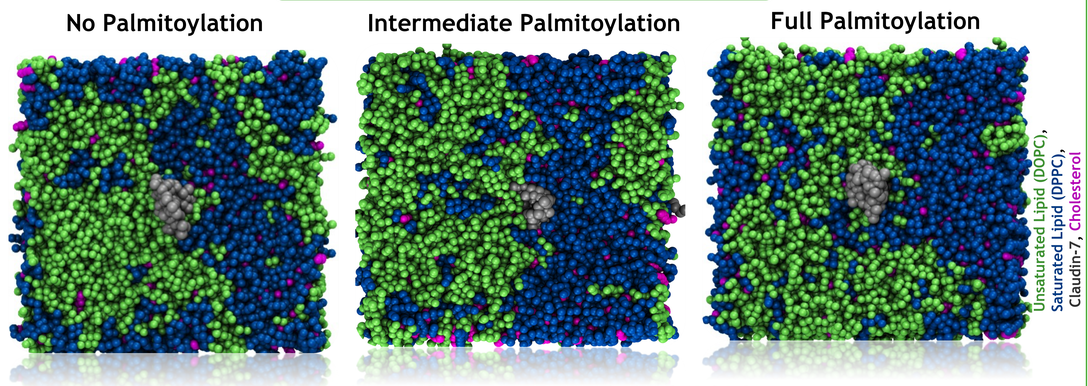
Methods

Coarse grained molecular dynamics simulations

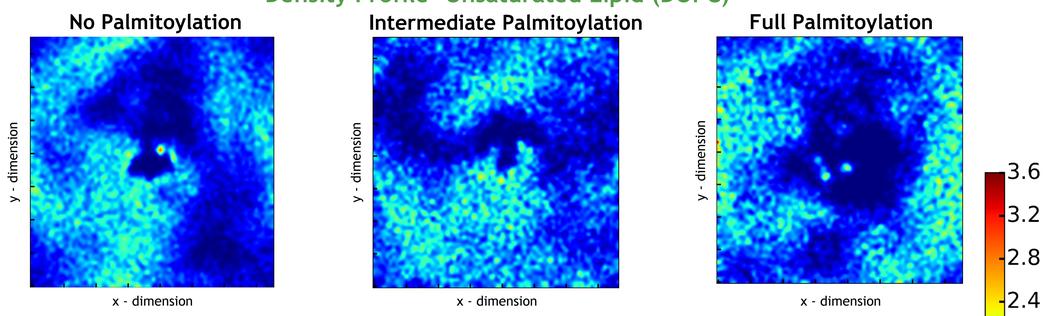
- MARTINI coarse grained force field
- GROMACS molecular dynamics package
- Claudin-7 with and without palmitoylation was studied
  - Intermediate: Cys 104 & 107
  - Full: Cys 104, 107 & 184
- Simulations were performed in triplicates for 10 microseconds each
- System solvated in 0.15 M NaCl
- Cell membrane composition- 2:2:1 ratio of saturated lipids (1,2-dipalmitoyl-sn-glycero-3-phosphocholine or DPPC), unsaturated lipids (1,2-dioleoyl-sn-glycero-3-phosphocholine or DOPC) and Cholesterol



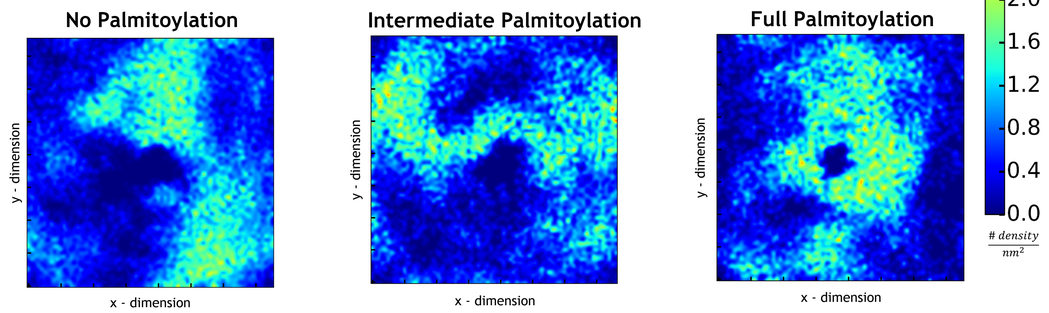
Results



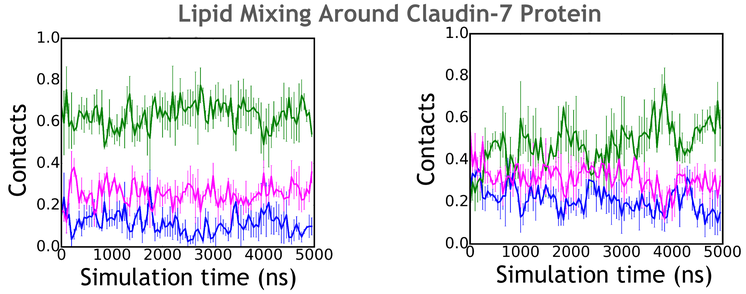
Density Profile- Unsaturated Lipid (DOPC)



Density Profile- Saturated Lipid (DPPC)



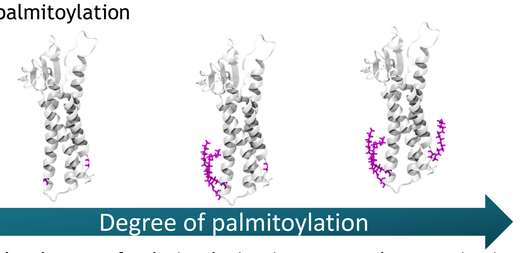
Lipid Mixing Around Claudin-7 Protein



Unsaturated Lipid (DOPC), Saturated Lipid (DPPC), Cholesterol (CHOL)

Conclusions

- Protein interaction with membrane lipids depends on its degree of palmitoylation



- As the degree of palmitoylation increases, the proteins interact more with the saturated lipids
- Non-palmitoylated proteins interact with unsaturated lipids
- Cholesterol localizes with saturated lipids
- Registration of the upper and lower leaflet of the membrane is affected by the presence of palmitoyl chains
- The observed trends were verified for six other Claudin proteins
- Overall, the study shows the importance of posttranslational modification of proteins and the impact on protein-membrane interactions

Future work

- Impact of palmitoylation on claudin-7 dimer formation
- Interaction of claudin-7 palmitoylation on membrane lipid with higher lipid diversity
- The role of palmitoylation in claudin-7 interaction with other members of the claudin family
- Impact of claudin-7 on the tight junction permeability

Acknowledgments

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References

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Membrane Protein's Behavior Changes Upon Palmitoylation