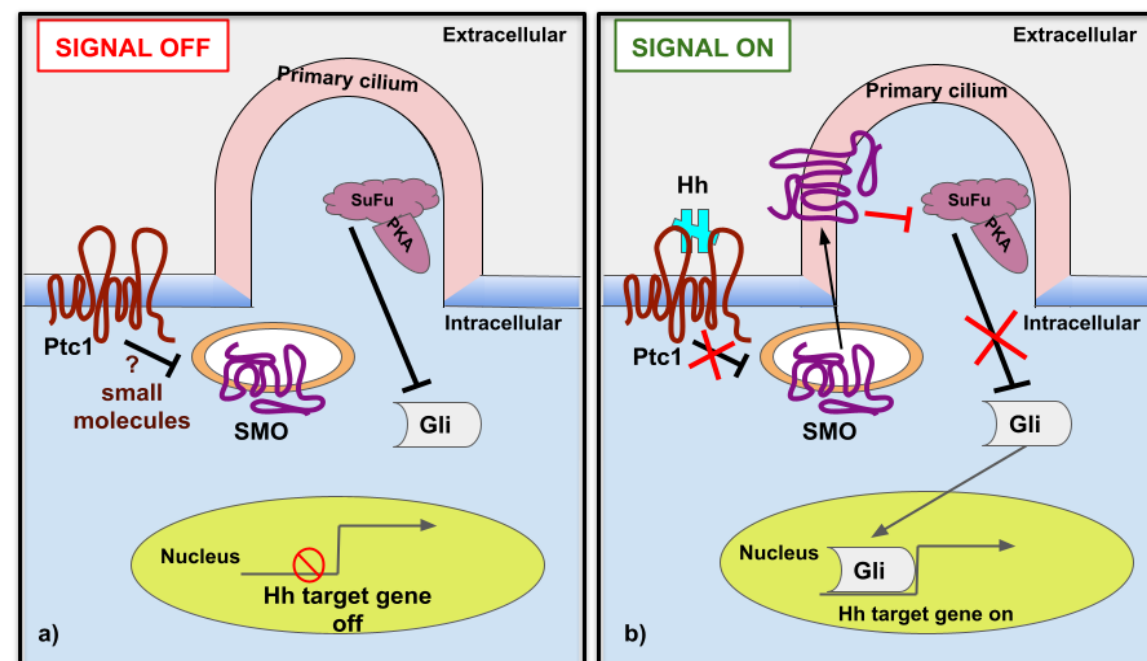


Structural modulation in Smoothed receptor (SMO) upon cholesterol binding

ABSTRACTS

- The Hedgehog (Hh) signaling pathway plays an important role in the growth and morphogenesis in many tissues. The aberrant Hh pathway activation is associated with developmental abnormalities, related serious diseases, and various types of cancers.
- In the absence of Hh, Ptc1 inhibits SMO, which allows SuFu and PKA to inhibit the Gli transcription factors (Fig. a). In the presence of Hh, Ptc1 stops inhibiting SMO and allows it to accumulate into the PI4P enriched primary cilium.
- SMO is now able to transmit the signal downstream, resulting in the transcription of target genes by Gli (Fig. b).



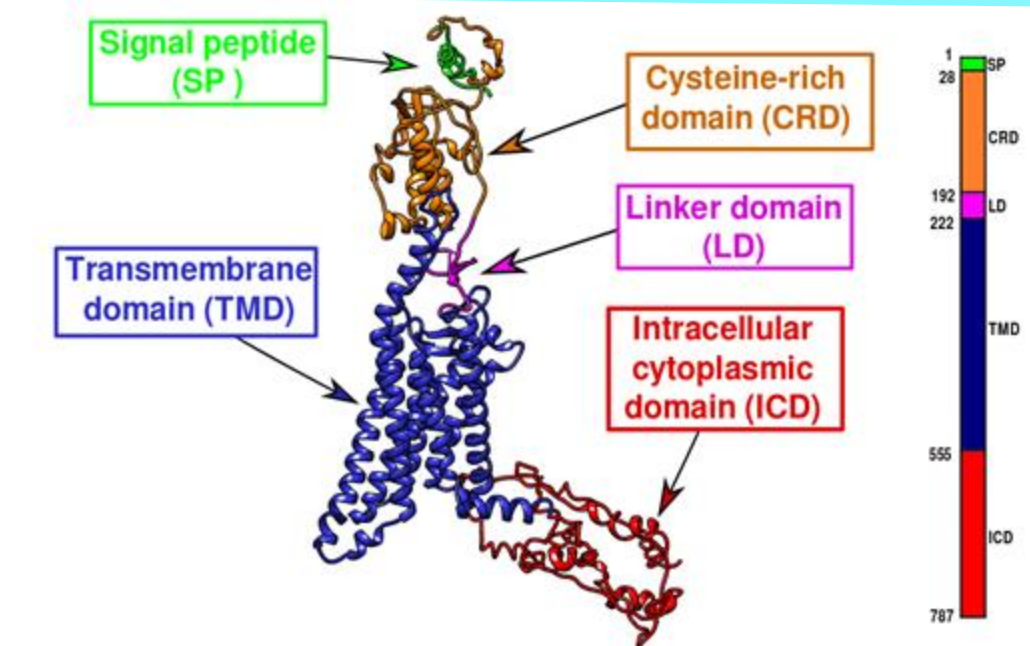
OBJECTIVE

- To study the structure, interaction and dynamics of SMO with cholesterol and other molecules in different model membranes.

METHODS AND MODELS

- 15 μ s long coarse-grained molecular dynamics simulations (using the MARTINI 2.1 force field with a 20 fs time step) of SMO in two model membranes.
- Physiologically relevant multi-component membranes to mimic the primary cilium.
- Tools and software: GPCR I-TASSER, CHARMM-GUI, GROMACS 2019 version, VMD.
- Basic structural analysis: root-mean-square deviation (RMSD), root mean square fluctuation (RMSF), radius of gyration, and solvent accessible surface area (SASA) and helical tilt
- Additional analysis: Dynamic cross-correlation maps (DCCM), Principal component analysis (PCA), Contact analysis.

RESULTS



- The interaction of membrane cholesterol with preferential sites in both TMD and CRD, respectively.
- SMO adopt multiple conformational states by changing CRD and ICD conformation.

SMO and membrane cholesterol interaction

