Frizzleds are dynamic, molecular machines

November 11 2021

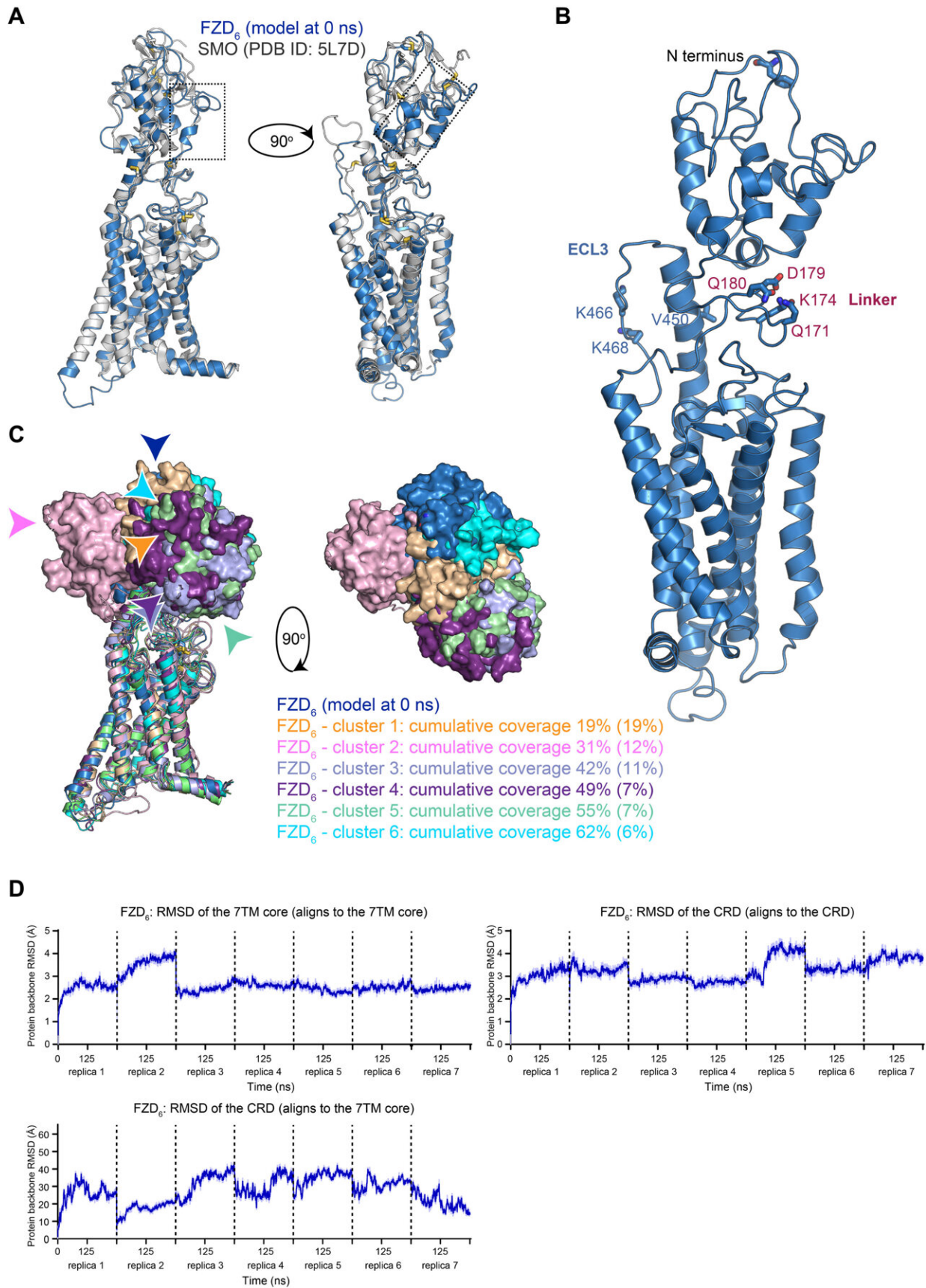**A**

FZD$_6$ (model at 0 ns)
SMO (PDB ID: 5L7D)

90°

B

N terminus

ECL3

K466

V450

K468

Q180

D179

Q171

K174 Linker

C

FZD$_6$ (model at 0 ns)
FZD$_6$ - cluster 1: cumulative coverage 19% (19%)
FZD$_6$ - cluster 2: cumulative coverage 31% (12%)
FZD$_6$ - cluster 3: cumulative coverage 42% (11%)
FZD$_6$ - cluster 4: cumulative coverage 49% (7%)
FZD$_6$ - cluster 5: cumulative coverage 55% (7%)
FZD$_6$ - cluster 6: cumulative coverage 62% (6%)

90°

D

FZD$_6$: RMSD of the 7TM core (aligns to the 7TM core)

FZD$_6$: RMSD of the CRD (aligns to the CRD)

FZD$_6$: RMSD of the CRD (aligns to the 7TM core)

Fig. 1. MD of FZD$_6$ and receptor model with amber codon placement.(A) Superimposition of the FZD$_6$ model (blue) and inactive SMO (gray; PDB ID: 5L7D). Disulfide bridges are shown as sticks. The dotted rectangles mark the extended linker region, which differs between these two structures. (B) A closer view to the FZD$_6$ model. Amino acid residues selected for the point mutations are marked as sticks. Color code is as follows: red, oxygen; dark blue, nitrogen; light blue, carbon; yellow, sulfur. (C) The CRD movements in the MD simulation. The receptor cores are shown as cartoon and CRDs as solid surfaces. Colored arrows mark the locations of the N termini of each conformation cluster. Cumulative percentage of the time of coverage for each position cluster in the MD (absolute percentage for each cluster in parentheses). (D) Protein backbone root mean square deviations (RMSDs) of the receptor core (amino acids 160 to 511) and the CRD (amino acids 1 to 130) plotted as a continuous simulation trajectory. Dotted lines mark the independent simulation replicas. Thick blue traces indicate the moving average smoothed over a 2-ns window, and thin traces indicate the raw data.

Maria Kowalski-Jahn and Hannes Schihada, two postdocs in the Schulte laboratory, have used a novel technology of fluorescently labeling receptors with a minimally invasive technique and detecting structural rearrangements in a receptor molecule in living cells. These experiments pinpointed how FZDs respond to WNT stimulation by conformational changes in the extracellular domain of the receptor. In contrast to what was previously surmised, but in line with several previous publications by the Schulte laboratory, these findings underline that WNT stimulation elicits conformational rearrangements in their receptors. These new insights into FZD dynamics present the basis for a continued mechanism-based drug discovery process to target FZDs for therapy.

Cell surface receptors are essential to transmit information from the outside of the cell to the inside to accomplish a physiological adaptation

in response to the perceived signal. This basic concept of cellular communication can be exploited by therapeutic intervention using drugs that either mimic the bodily molecule activating the receptor (agonists) or interfere with binding of the bodily molecule as so-called antagonists. Irrespectively, the dynamic process of receptor activation can only be targeted if it is understood in its basic details. The Schulte laboratory works on Class F G protein-coupled receptors including Frizzleds, which are seen as attractive drug targets for example for cancer therapy. So far, however, the molecular underpinnings of ligand (WNT)-induced FZD activation remains obscure.

This study is published in *Science Advances*.

Provided by Karolinska Institutet