ABSTRACT

The Balance Model explains Ras-Isoform Specificity by Sequence Variations on Helix alpha-4 and the Hypervariable Region

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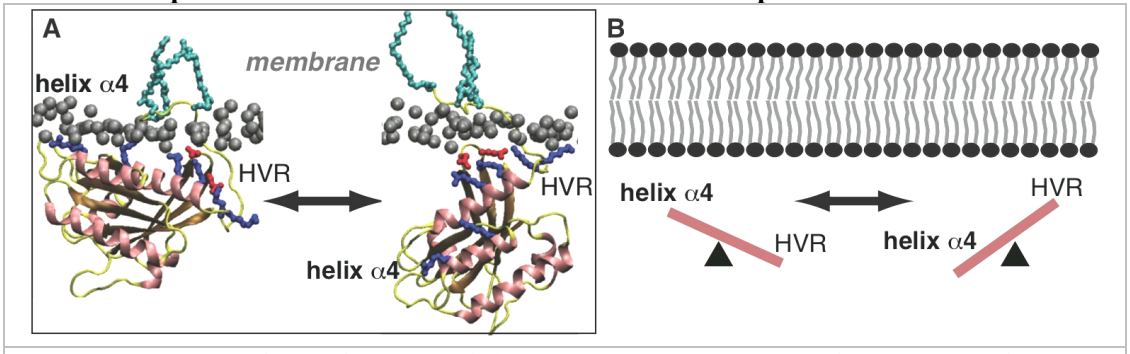
Small GTPases of the Ras superfamily are central to critical cellular functions, such as proliferation, differentiation, migration and trafficking. Therefore, their misregulation is associated with severe diseases. More than 150 Ras-like GTPases are known, which are divided into four major subfamilies. Each of the subfamilies contains between 22 to 63 structurally related, but functionally distinct isoforms. For almost two decades, the lipid modified C-terminal *H*yper*V*ariable *R*egion (HVR) of small GTPases was recognized as the primary structural determinant for isoform specificity. However, a mechanistic explanation as to how the HVR realizes this was missing.

Using a combination of computational biology, molecular cell biology and quantitative fluorescence imaging techniques, we recently provided new structural insight on how Ras operates in the context of the membrane. We provided evidence that Ras adopts isoform specific orientations on the membrane, which in turn critically regulate Ras activity. These orientations are guided by a new switch III region and are stabilized by the amphipathic helix alpha-4 and the C-terminal HVR. We propose the 'balance model', where different combinations of the HVR and helix alpha-4 tune the membrane orientation equilibrium of small GTPases to direct isoform specific functions.



The balance-model for isoform specificity – the missing structure-function link for small GTPases? (A) The two computationally simulated conformers of membrane anchored H-Ras are primarily stabilized either by helix alpha-4 (left) or the HVR (right). (**B**) Schematic representation of the equilibrium, where the orientation of the G domain is represented by a 'balance'-bar. Our **balance-model** explains that the conformational equilibrium depends on the relative membrane affinities of the HVR and helix alpha-4, which differ among the Ras isoforms. The specific equilibrium then profoundly influences downstream interactions and signalling. We propose that this mechanism also operates in other members of the Ras-superfamily.

References:

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