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Use of docking tools and MD simulations to predict the interaction between the MH2 domain of Smad3 and the PDZ domain of Erbin

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Short Abstract: Erbin has been identified as a binding partner for Smad3, a major component of the transforming growth factor-beta signaling pathway. We present how the use of bioinformatics and molecular modelling tools such as molecular dynamics helped us to conceptualize the association between the Smad3 MH2 and Erbin PDZ domains.

Long Abstract:

Erbin was originally identified as a protein that interacts with the receptor tyrosine kinase ErbB2 (also known as HER-2 or Neu) and plays a role in its signalling activity in epithelial and neuronal cells. This protein contains 16 leucine-rich repeats in its amino terminus and a PDZ domain in its carboxy terminus. PDZ domains are widely distributed protein-protein interaction domains in the human genome. In humans, about 540 PDZ domains are present in proteins that have signalling, scaffolding and regulatory functions. Recently, Erbin has been identified as a binding partner for Smad3, a major component of the transforming growth factor-beta (TGF beta) signaling pathway. The Smad proteins constitute a family of intracellular proteins that function as signal transducers for the TGF beta superfamily. The eight human Smads, Smad1 to Smad8, can be grouped into three subfamilies: the receptor-regulated Smads (R-Smads), the common Smads (Co-Smads) and the inhibitory Smads (I-Smads). Smad3 shares a common domain organization with other R-smads and Smad 4, consisting in an amino-terminal DNA-binding domain (MH1 domain) and a carboxy-terminal effector domain (MH2 domain) separated by a linker region. The MH2 domain is a versatile protein-protein interaction module interacting with a long list of partners. It has been discovered that Erbin and Smad3 form a protein complex in vivo and directly interact in vitro. However it remains to determine the modalities of interaction between Erbin and Smad3 at the molecular level. Biochemical experiments demonstrate that the MH2 domain of Smad3 is required for this interaction, and that the carboxyterminal region of Erbin encompassing residues 914 to 1257, plus the PDZ domain are involved in this interaction. Furthermore, a mutagenic analysis has shown that the classical binding pocket of the PDZ domain plays no role in the interaction. In this poster, we present how the use of the bioinformatic and molecular modelling tools (alignments and structure analysis programs) helped us to conceptualize the association between the Smad3 MH2 and the Erbin PDZ domains and to propose a model for the association of the two partners. Additionally, we used the ClusPro automatic docking web server to create another model association that agrees with the few available experimental datas. We then carried out a

molecular dynamic of 20 ns for the two models of association to evaluate their stability. These molecular dynamics calculations show that the two models converge to a unique position in which we defined key residues in both Smad3 and Erbin important for the interaction. We are currently in the process to mutate these residues to validate our proposal.