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Meeting abstract

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Structural basis for the oncogenic signalling complex formed by Grb2 and Gab2 in Her2 (ErbB2/Neu)-driven breast cancers and CML cells

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The adaptor protein Grb2 and the large multi-site docking protein Gab2 form a complex that is crucial for the oncogenic signalling of some cancer cells. Binding of the C-terminal SH3 (SH3C) domain of Grb2 to Gab2 is essential for the interaction, but molecular details of the complex formation have remained undefined. Using peptide array SH3 overlay blots, isothermal titration calorimetry and protein crystallography, two atypical SH3 domain binding sites in Gab2 (Gab2-1 and Gab2-2) were confirmed and characterised. Gab2-1 has considerable similarity to an epitope in the cell cycle regulator p27Kip1 that also binds Grb2SH3C. The SH3C binding sites in Gab2 differ approximately 5-fold in their affinity and also with respect to the residues important for the interaction apart from a shared core motif RxxK. Both SH3 domain interaction sites in Gab2 are conserved throughout evolution and found, for example, in the Gab homolog *daughter of sevenless* (Dos) of *Drosophila melanogaster*, which binds to the Grb2 homolog Drk. Mutagenesis of the Drk binding sites in Dos *in vivo* impairs fly eye and wing vein development and documents that both sites are functionally important. A high-resolution crystal structure was generated of the Gab2-2 epitope in complex with the Grb2SH3C domain. This reveals a binding mode reminiscent of the interaction of haematopoietic Grb2-relative Mona/Gads with the T-cell adaptor SLP-76 and haematopoietic progenitor kinase 1 (HPK1). However, subtle differences exist, which could potentially be exploited to generate SH3C domain inhibitors with preference for a specific Grb2 family member.