s8a.m8.o5 **X-ray structures of complexes of SH2-Grb2 domain with high affinity inhibitors**. P. Nioche[a], W.Q. Liu[b], I. Broutin[a], M. Vidal[b], C. Garbay[b], A. Ducruix[a]. [a] *Laboratoire de Cristallographie et RMN Biologiques - CNRS EP 2075* [b] *Laboratoire de Pharmacologie Moléculaire et Structurale - INSERM U266-CNRS UMR8600 Faculté de Pharmacie - Université René Descartes 4, Avenue de l'Observatoire 75270 Paris cedex 06 FRANCE*
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It has been over a decade since mutated *ras* genes with oncogenic properties were first described in human tumors and knowledge in Ras signalling has largely increased since this time. The activation of the growth factor receptor induces phosphorylation of tyrosine residues of its C-terminal part, creating binding sites for Grb2 SH2 domain. Grb2 is an adaptor protein, which recruits Sos, the exchange factor of Ras. Recruitment of Sos facilitates Ras activation and subsequent signal transmission down the Ras dependent kinase cascade, which then transduces signals into the nucleus by activating early transcription factors.

The structure of Grb2, a 25 kDa adaptor, is composed of one SH2 and two SH3 domains and is a good example of a bifunctional protein[1]. Grb2-SH2 domain binds to class II phosphotyrosyl peptides with consensus sequence pYXNX.

To study the interaction between Grb2 and phosphorylated Grb2 inhibitors, we have solved the structures of complexes between Grb2-SH2 domain and peptides corresponding to Shc derived sequences. Three structures of complexes will be presented : SH2-Grb2/PSpYVNVQN (1.5Å), SH2-Grb2/ mAZ-pY-(αMe)pY-N-NH_2 (2Å) and the native SH2 (2.7Å). Data were collected at ESRF/ID14 at Grenoble and EMBL/Daisy at Hamburg.

The mAZ-pY-(αMe)pY-N-NH_2 pseudo-peptide shows a nanomolar affinity for Grb2[2]. This high affinity was related to new interactions with non conserved residues, as shown by X-rays.

Notes

[1] S. Maignan et al. Crystal structure of the mammalian Grb2 adaptor. *Science* (1995), **268**, 291-293.
[2] W.Q. Liu et al. Small peptides containing phosphotyrosine and adjacent alphaMe-phosphotyr or its mimetics as highly potent inhibitors of Grb2 SH2 domain. J. Med. Chem. (1999) **42**, 3737-3741.