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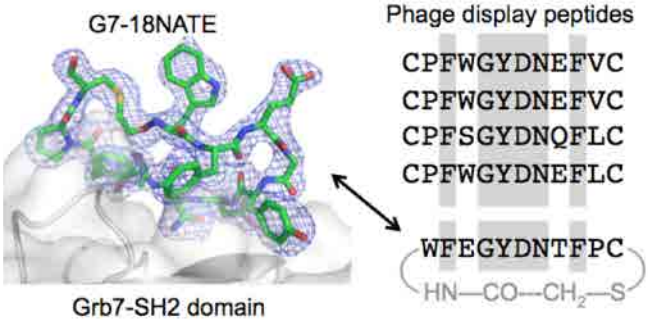
Growth factor receptor bound protein-7 (Grb7) is an adapter protein, aberrantly overexpressed in several cancer cell types, that mediates the coupling of tyrosine kinases with their downstream signalling pathways via its SH2 domain. In particular, Grb7 signals the activation of the erbB-2 receptor, which plays a key role in the progression of poor prognostic breast cancers. Grb7 is over-expressed with erbB2 in a subset of human breast cancer cell lines and breast tumours, suggesting erbB2 signaling via Grb7 may be increased in these cancers. Grb7 also mediates signalling pathways from focal adhesion kinase (FAK) in the regulation of cell migration, also implicated in tumor progression. It is thus a prime target for the investigation of the potential of novel anti-cancer therapies. We are currently examining Grb7-SH2-specific cyclic peptides developed using phage display libraries using biophysical techniques. Structural and affinity measurements for the Grb7-SH2 domain, as well as computational approaches are being used to develop more potent and specific molecules. Cellular studies of cell-permeable forms of these peptides will allow us to better understand the downstream effects of Grb7 and to serve as a starting point in the design of therapeutics targeting Grb7.

Research Projects

1. Targeting the Grb7 protein involved in cancer progression



Grb7-SH2 domain/inhibitor complex

OTHER PROGRAM AFFILIATIONS

Infection and Immunity

Neuroscience

Selected significant publications:

1. Watson GM, Gunzburg MJ, Ambaye ND, Lucas, WA, Traore DA, Kulkarni K, Cergol KM, Payne RJ, Panjikar S, Pero SC, Perlmutter P, **Wilce MCJ** and **Wilce JA**. 2015 Cyclic peptides incorporating phosphotyrosine mimetics as potent and specific inhibitors of the Grb7 breast cancer target. *Journal of Medicinal Chemistry* 58, 7707-7718.
2. Kim HS, **Wilce MCJ**, Yoga YMK, Pendini NR, Gunzburg MJ, Cowieson NP, Wilson GM, Williams BR, Gorospe M and **Wilce JA**. 2011. Different modes of interaction by TIAR and HuR with target RNA and DNA. *Nucleic Acids Research* 39, 1–14.
3. Ambaye ND, Pero SC, Gunzburg MJ, Yap M-Y, Clayton DJ, Del Borgo MP, Perlmutter P, Aguilar M-I, Shukla GS, Peletskaya E, Cookson MM, Krag DN, **Wilce MCJ** and **Wilce JA**. 2011 Structural basis of binding by cyclic non-phosphorylated peptide antagonists of Grb7 implicated in breast cancer progression. *Journal of Molecular Biology.* 412, 397-411.
4. Kim HS, Kuwano Y, Zhan M, Pullmann R Jr, Mazan-Mamczarz K, Li H, Kedersha N, Anderson P, **Wilce MC**, Gorospe M, **Wilce JA**. 2007. Elucidation of a C-Rich Signature Motif in Target mRNAs of RNA-Binding Protein TIAR. *Mol Cell Biol.* 27, 6806-6817.
5. **Wilce JA**, Vivian JP, Hastings AF, Otting G, Folmer R, Duggin IG, Wake RG and **Wilce MCJ**. 2001. Structure of the RTP/DNA complex and the mechanism of polar replication fork arrest. Nature *Structural Biology* 8, 206-210.