

The WW domain, (also known as the rsp5-domain or WWP repeating motif) is a modular protein domain that mediates specific interactions with protein ligands. This domain is found in a number of unrelated signaling and structural proteins and may be repeated up to four times in some proteins.

Apart from binding preferentially to proteins that are proline-rich, with particular proline-motifs, [AP]-P-P-[AP]-Y, some WW domains bind to phosphoserine- phosphothreonine-containing motifs.

The first structure of the WW domain was determined in solution by NMR approach.

It represented the WW domain of human YAP in complex with peptide ligand containing Proline-Proline-x-Tyrosine (PPxY where x = any amino acid) consensus motif.

The YAP WW domain structure in complex with SMAD-derived, PPxY motif-containing peptide was further refined.

Apart from the PPxY motif, certain WW domains recognize LPxY motif (where L is Leucine), and several WW domains bind to phospho-Serine-Proline (p-SP) or phospho-Threonine-Proline (p-TP) motifs in a phospho-dependent manner.

Structures of these WW domain complexes confirmed molecular details of phosphorylation-regulated interactions.

There are also WW domains that interact with polyprolines that are flanked by arginine residues or interrupted by leucine residues, but they do not contain aromatic amino acids.

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