FBXO44-Mediated Degradation of RGS2

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G Protein Coupled Receptor (GPCR) signaling plays a key role in intercellular communication and regulates many physiological processes relevant to disease. Approximately 30-40% of all FDA approved drugs target GPCR pathways, but limitations and off-target side effects remain obstacles. Regulator of G protein Signaling (RGS) proteins negatively modulate GPCR signaling by accelerating deactivation of the Gα subunit and thus represent a novel alternative to current approaches. While research on RGS proteins and how they are regulated has expanded rapidly, there are still gaps in knowledge for some members of the RGS family. One example is RGS2, which is selective for $G\alpha_q$ signaling. Lowered RGS2 levels are implicated in numerous diseases, and while the E3 ligase responsible for facilitating degradation of RGS2 has been identified more work needs to be done to viably drug it to enhance RGS2 protein levels. We explore how FBXO44, an E3 ligase substrate recognition component responsible for RGS2 degradation, interacts with RGS2 to explore approaches to inhibit degradation.

While the FBXO44-RGS2 interaction has been demonstrated previously, the degron sequence of RGS2 remained unknown. We hypothesized that FBXO44 binds RGS2 at its N-terminus and investigated this using N-terminally truncated RGS2 constructs. Our results indicated that FBXO44 binds between residues 5 and 16 of RGS2, as removal of these stabilized RGS2 against proteasomal degradation. Based on these results we designed a peptide microarray to identify important residues and properties for FBXO44 *in vitro* and found that Cys^{13} is essential for FBXO44 binding.