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Comparison of the modulation of FGFR signalling by thalidomide and its analogs lenalidomide and pomalidomide

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Abstract

Thalidomide, a powerful teratogen, re-emerged as a wonder drug for its teratogenic, anti-angiogenic and anti-tumor properties. Being FDA approved for Multiple Myeloma along with the analogs lenalidomide and pomalidomide is currently being tested in more than 2000 clinical trials for a range of conditions including solid tumors and inflammatory disorders. Fibroblast growth factor receptors (FGFRs) play key roles in embryonic development and cancer. There are indications that thalidomide might be linked to FGFR biology, however no experimental evidence is available till now.

To understand the effects of thalidomide and its analogs, lenalidomide and pomalidomide, we utilized *in silico* predictive tools, kinome profiling, transcriptome and phosphoproteome tools to study the modulation of FGFR signalling in endothelium. Genecodis and Enrichr with the differentially expressed genes were used to obtain the Gene Ontology, Transcription factor, Pathway and miRNA enrichments. The association of the drug with FGFR signalling was investigated at various levels. Protein-chemical network tool, STITCH and Pocketome predicted strong association of thalidomide with FGFR2. At gene expression level, FGFR1 and FGFR2 were found to be affected under the three drug treatments in *in vitro* and *in vivo* models. Kinomescan results suggest the binding of thalidomide with high affinity to a mutant FGFR3 (G697C) and FGFR2. To validate this, we checked the activity of FGFR2 kinase under the three drug treatments and found that they affected the kinase activity in a dose-dependent manner with pomalidomide having lowest IC_{50} value. Blind docking using Autodock revealed the possible binding sites and interestingly all the three analogs were predicted to bind to Lys517 of FGFR2. Lys517 is one of the ATP binding sites, suggesting that possibly analogs interfere with the ATP binding. Taken together, FGFRs could be potential targets of thalidomide and its analogs and the modulation of FGFRs by thalidomide partially explain the teratogenic and anti-tumor properties of the drug. Thus through different platforms, the mechanisms of drugs could be understood in a better way. This in turn will aid in modifying the drug structures resulting in the development of new analogs with more efficacies and reduced undesired effects.

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