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In silico analysis of enantioselective binding of IMiDs to cereblon

Thalidomide and its analogs, lenalidomide and pomalidomide (referred to as immunomodulatory drugs or IMiDs) have been known to treat multiple myeloma and other hematologic malignancies as well as to cause teratogenicity. Recently the protein, named cereblon, was identified as the primary target of IMiDs and crystallographic studies of the cereblon-IMiD complex showed strong enantioselective binding for the (S)-enantiomer of IMiDs. Here, using the structures of cereblon and IMiDs (both (S)-enantiomers and (R)-enantiomers), we performed docking simulations in order to replicate this enantiomeric selectivity and to identify the region(s) contributing to this selectivity. We confirmed the enantioselective binding of IMiDs to cereblon with high accuracy, and propose that the hairpin connecting the β10-β11 region of cereblon (residues 351-355) contributes to this selectivity and to the increased affinity with IMiDs. Our docking results provide novel insights into the binding mode of IMiDs-like molecules and contribute to a deeper understanding of cereblon-related biology.

Biography

Tatsuya Takagi has completed his PhD from Osaka University. At that time, he had been an Assistant Professor in the School of Pharmaceutical Sciences, Osaka University for 5 years. Then, since 1993, he had worked for the Genome Information Research Center, Osaka University as an Associate Professor until he became a Professor of Graduate School of Pharmaceutical Sciences, Osaka University in 1998. He has published more than 100 papers in reputed journals and serving as Chairman of Division of Structure-Activity Relationship of the Pharmaceutical Society of Japan.

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