GÖTEBORGS UNIVERSITET

Modeling and exploring human IRE1 as a strategy to design novel inhibitors: a computational approach

Antonio Carlesso
Institutionen för kemi och molekylärbiologi
Naturvetenskapliga fakulteten

Akademisk avhandling för filosofie doktorsexamen i kemi, som med tillstånd från Naturvetenskapliga fakulteten kommer att offentligt försvaras fredag den 31 01 2020 kl.10.00 i Waldemar Sjölander, Institutionen för kemi och molekylärbiologi, Medicinaregatan 7A, Göteborg.

ISBN: 978-91-7833-754-5 (PRINT)
ISBN: 978-91-7833-755-2 (PDF)
http://hdl.handle.net/2077/62404

GÖTEBORGS UNIVERSITET

ABSTRACT: Inositol Requiring Enzyme 1 (IRE1) is a bifunctional serine/threonine kinase and endoribonuclease that is the major mediator of the Unfolded Protein Response (UPR) during endoplasmic reticulum (ER) stress. The association of IRE1 dysregulation with a wide range of human diseases, stimulated research towards the discovery of small organic molecules able to modulate IRE1 signalling, and to potentially be used as novel therapeutics.

In this thesis we performed *in silico* three-dimensional (3D) molecular modeling analyses encompassing: (i) the selection of suitable protocols for docking and virtual screening in the IRE1 serine/threonine kinase and endoribonuclease domains studies, (ii) the exploration of IRE1 and PERK ligand interaction networks, (iii) the study of IRE1-ligand recognition phenomena in order to understand the mechanism of action of IRE1 small organic modulators and (iv) offers important insights relevant to hit-discovery and lead optimization of novel IRE1 modulators.

Our structure-based drug design approach provides useful information for designing improved IRE1 ligands, as confirmed by one soon-to-be-filed patents on new inhibitors targeting IRE1, developed during the PhD period.

KEYWORDS: ER stress, unfolded protein response, cancer, inflammation, neurodegeneration, therapeutic targets, molecular docking, molecular dynamics.