RESEARCH PROJECT

STRUCTURAL CHARACTERIZATION OF DISEASE-SPECIFIC RELATED CK2A KINASE COMPLEXES AND MUTANTS

CK2 is a S/T protein kinase, whose aberrant activity is related to a plethora of human diseases, ranging from cancer to virus infections and psychiatric disorders. It is a constitutively active enzyme, with no obvious mechanism of regulation, and, although in many cases its pathologically high activity can be explained by a high CK2 protein level, the reasons of its abnormal up-regulation are largely unknown. It has been reported that CK2 association to specific binding proteins may enhance its activity, but a detailed investigation on this possible mechanism of regulation has never been performed.
Beside up-regulation, mutations of the CK2 gene CSNK2A1 have been recently described in the neurodevelopment disorders Okur-Chung (OCNDS). Only preliminary biochemical characterization of some of these mutants has been reported. We produced some of them, and preliminary results show they have impaired activity.
The aim of this project is to develop a novel platform based on protein immobilization a well as advanced crystallization and characterization techniques to perform structural/functional studies on:
1. CK2 complexes with cellular proteins expected to produce an activator effect. This would allow to design molecules preventing/disrupting such interactions, thus protecting against aberrant activation of CK2 and by simulating the interacting regions, to obtain small CK2 activator molecules, useful in case of too low CK2 activity;
2. CK2 natural mutants recently found in OCNDS patients, to characterize the biochemical properties and possible conformational changes of relevant cases, with respect to the wild-type protein, and explore hypotheses of future therapeutic interventions.
The research activities planned in this project include stability and morphological studies on selected CK2-activator partners, crystallization and structural determination of the most stable CK2-complexes and its natural mutants by X-ray diffraction and/or by complementary in solution techniques such as Small Angle X-ray Scattering and Cryo-Electron Microscopy
The achievements of this project are expected to have a high impact in biomedical field aiming not only at improving the knowledge on a kinase strongly implicated in diseases, but also at identifying new possible therapeutic strategies.