"In search of molecular mechanism of gastric cancer cell response to FGFRinhibitor"

Dima Antoun, Molecular Enzymology department, Intercollegiate Faculty of Biotechnology UG-MUG

Supervisor: dr hab. Rafał Sądej

Gastric cancer is still posing a major challenge. Therefore, it is very important to find prognostic markers predicting patients response to new drugs. Members of fibroblast growth factor receptors family (FGFR1-4) consist of an extracellular ligand domain that is comprised of three immunoglobulin like-domains, a single transmembrane helix domain and an intracellular part with a tyrosine kinase activity. The later, when it gets phosphorylated it recruits adaptor proteins involved in signal transduction, and this triggers a number of cellular responses such as cell growth, differentiation, apoptosis and survival.

During my PhD project I currently aim to find protein markers of gastric cancer cell response (both positive and negative) to FGFR inhibitor (cpl 304-110-01) designed and synthesized by 'CelonPharma'. Firstly I tested various gastric cancer cell lines (SNU-16, SNU-1, SNU-5, Kato-III, and AGS) proliferation at the presence of inhibitor with classical assays (SRB and MTT). Snu-16 and Kato-III cells very strongly responded to the inhibitor (impaired growth) with IG50 0,03μM and 0,04μM, respectively. On the other hand, AGS, SNU-1, SNU-5 are rather non-responsive to the compound and grew even at the concentration of 5μM of the drug.

To find a potential marker of cell response to FGFR inhibitor, a broad panel of proteins was analysed. These involve molecules which belong directly to FGFR-triggered signalling (FRS2, PLCy, AKT, ERK), - are positive or negative regulators of FGFR pathway (Spry2, Shp2, GSK3beta, PKC), - are involved in gastric cancer progression (Src, HER2),- are markers of epithelial mesenchymal transition (N- and E-caherin, vimentin, HSP27), - were shown to be associated with other FGFR inhibitors (c-myc). We found that FGFR2 is the only member of FGFR family expressed in gastric cancer cell lines.

To precise a mechanism of cell response to FGFR inhibitor, I derived variants of sensitive cell lines (SNU-16 and Kato-III) which are resistant to compound. They will be used as additional tool to define potential markers predicting gastric cancer cell response to FGFR inhibitor.

HUMAN CAPITAL
NATIONAL COHESION STRATEGY

Project co-funded by European Union under the European Social Fund