

Can computer models based on fundamental laws assist the treatment for cancers?

Over the last decade, scientists have been intensely investigating on TRAIL, a protein released by our immune system, to treat malignant cancers. The benefit of using TRAIL, as compared to conventional chemo- or radiotherapies, is that it specifically destroys carcinomas without affecting the surrounding normal tissues. This is done through a mechanism known as the programmed cell death or apoptosis. However, the TRAIL-based treatments so far have not been overtly successful as many carcinomas are able to ‘cheat’ the death signal, triggered by the TRAIL, into a survival signal.

A team of scientists from the Keio University in Japan have formulated a method using a computational model and, with its aid, predict a novel target that would in return cheat the cancer cells to switch from survival to apoptosis mode. The work of Dr Kumar Selvarajoo and colleagues, utilizing the fundamental physical law of conservation, pinpoints an intracellular target, whose removal will reroute most of the resultant signaling flux of TRAIL into a predetermined direction along the caspases-induced death pathway. Their findings are published in Scientific Reports, a newly launched journal of the Nature Publishing Group.

"Cancer biologists focus either to suppress the cell survival pathways or to enhance the apoptosis mechanisms independently. We felt a systemic approach considering both processes at the same time is necessary. Our previous experience working on the Toll-like receptor signaling models, based on fundamental physical rules, helped us to identify a target at the crossroad of the survival and apoptosis pathways in TRAIL signaling." said Dr Selvarajoo, the team leader for the research.

Vincent Piras and Kentaro Hayashi, joint first authors for the study, say that the currently known signaling process of TRAIL is insufficient. "First, we developed a computational model to match experimental data with simulations. We found that the topology we know of TRAIL's downstream signaling needs to be adjusted in order to make trustable simulations. We modified the crosstalk very carefully with response rules and checked it with biological plausibility. In total, we had to make three major insertions. Adding this information into our model, we were able to simulate accurately the key survival and death molecules in wildtype and several mutant cancer cells. To our knowledge, this is the first time a single computational model can simulate multiple experimental conditions", says Vincent Piras, a final-year doctoral student.

The scientists predict that a novel molecule interacting with p62 could be a crucial target for enhancing apoptosis of TRAIL-resistant cancer. "Although we suggest this, experimental validation is required for final confirmation as a next step. Nevertheless, using the law of nature to address biological problems could potentially revolutionize the way we understand and treat complex diseases such as cancer and inflammation. In this respect, we feel very optimistic", says Kumar Selvarajoo.

