A NEW STRATEGY FOR CANCER CHEMOTHERAPY

Madrid, November 28th, 2011- The latest work from the Genomic Instability Group at the Spanish National Cancer Research Centre (CNIO), led by Óscar Fernández-Capetillo, is published today in the prestigious journal *Nature Structural and Molecular Biology*.

The manuscript, in which the CNIO Groups of Dr. Mariano Barbacid and Dr. Manuel Hidalgo, as well as the Group of Dr. Bruno Amati at the Italian FIRC Institute of Molecular Oncology (IFOM) have participated, describes a new strategy that allows a selective killing of cancer cells, given that the tumours present a particular feature. One of the main limitations of current cancer therapy is that the treatment usually is not only toxic for the tumour, but also for the healthy tissue. This is the source of the widely known off-target effects of radio- and chemotherapy; which may significantly affect the patients’ health. In this context, many of the current efforts are dedicated to the discovery of chemicals that are particularly toxic for cells harbouring cancer-associated mutations. Besides the presence of mutations, another approach is whether the therapy could exploit a more generic feature of cancer cells.

In 2005, several groups reported that a number of cancers present elevated levels of replicative stress, a kind of stress that derives from a deficient DNA replication. During the last 5 years at the CNIO, the group of Dr. Fernández-Capetillo has focused its research in the understanding of what replicative stress is, and in the investigation of the cellular mechanisms that protect from this stress. In what refers to cancer, the group has been elaborating on a simple idea: “if –and only if– cancers present high levels of replicative stress, then they might be particularly sensitive to chemical inhibitors that eliminate the cellular protection against replicative stress”.

In an article led by Matilde Murga as first author, the group now describes that tumours harbouring high levels of replicative stress are particularly sensitive to the genetic or chemical inhibition of ATR and Chk1 kinases. These two kinases are the key initiators of the cellular defense against replicative stress, which would explain the high sensitivity of the tumours. As proof of concept, the group shows that Chk1 inhibitors are very effective for the treatment of Burkitt lymphomas, which present high levels of replicative stress. In contrast, this treatment is largely ineffective for the treatment of tumours with no detectable amounts of this stress. In addition to the chemical inhibitor data, the article also shows that limited levels of ATR completely prevent the development of lymphomas and pancreatic tumours initiated by Myc oncogenes, both of which are characterised with high levels of replicative stress.

Part of the relevance of this work is due to the fact that some of these molecules (i.e. Chk1 inhibitors) were already being tested in the clinic for cancer chemotherapy. However, the results so far were modest and only a few patients showed a positive response. The work of Fernández-Capetillo now helps us to understand this poor efficacy, and provides a rationale to identify which patients are most likely to respond to the treatment. The article ends proposing that the use of ATR and Chk1 inhibitors in the clinic should be restricted to the treatment of tumours that present high levels of replication stress.

In relation to this same line of work, the group recently reported the development of chemical
ATR inhibitors –entirely done at the CNIO– and which showed interesting anti-neoplastic properties in vitro (Toledo et al. *Nat Struct Mol Biol* 2011). In collaboration with the Experimental Therapeutics Programme at the CNIO, the group is now trying to further develop these molecules into actual drugs that could be tested in the clinic for their antitumoural properties.

References:
