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Team finds possible new pharmacological target for one of the most important and elusive oncogenes

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The MYC oncogene intervenes in many types of cancer, some of which are very aggressive; researchers suspect that controlling its activity could open avenues to new treatments. However, MYC is an especially complex oncogene that has resisted therapeutic manipulation to date. Researchers of the Spanish National Cancer Research Centre (CNIO) have now managed to identify a protein that is essential for MYC to cause cancer in mouse models, and they believe that it could be a new target for future anti-cancer drugs. The paper, which has been published today in *Nature Communications*, uses genome wide data analysis techniques to study the behaviour of MYC in networks that consist of hundreds of genes.

MYC is one of the main proteins that regulate gene expression in cells. Most of these proteins act on less than 1 per cent of the genes in the genome, but MYC regulates between 2,000 and 3,000 genes, which accounts for up to 15% of the genes in the entire genome. Consequently, MYC intervenes in a plethora of cellular functions: cellular growth, proliferation, differentiation and apoptosis.

As mentioned by Paco Real, head of the CNIO's Epithelial Carcinogenesis Group, and one of the authors of the paper, "MYC is really a general controller of cell activity; it is one of the few genes that, if eliminated, makes cells unviable."

We know that, when it is deregulated, MYC promotes the formation of multiple types of cancer—pancreas, ovary, colon, lymphomas, among others —. The MYC gene is altered in more than half of human cancers, and it is often associated with very aggressive tumours.

That is the reason why many groups have long sought to target MYC, with the idea that inhibiting it would constitute a new way of fighting cancer. However, the complicated manner in which it operates makes this oncogene a difficult target.

The CNIO's Epithelial Carcinogenesis Group resorted to genome wide data analysis strategy. Working with cells cultured in vitro and bioinformatic tools, they managed to identify a gene, called BPTF, as a potentially important gene in cancer.

Cells Do Not Grow When BPTF Becomes Inactive

The researchers also detected mutations in BPTF in bladder cancer, and subsequently showed that when BPTF is made inactive, cells are unable to grow. This suggested a function related with MYC.

As Real explained, "we saw that when we perturbed the function of BPTF, this affected many genes that are known to depend on MYC; this led us to think that MYC needs BPTF for its biological functions."

Indeed, in a mouse model of pancreatic cancer dependent on MYC, Real's Group, in collaboration with the CNIO's Molecular Cytogenetics Unit headed by Juan Cruz Cigudosa, showed that inhibiting the action of BPTF reduces the aggressiveness of the tumours.

BPTF, therefore, appears as an important link in the chain of molecular events that allow MYC to function. The study showed that by blocking BPTF, tumour cells do not proliferate or their proliferation is reduced;

therefore, the authors considered that this gene could be a new target to treat many types of cancer.

"We propose that a valuable approach to treating MYC-dependent tumours is to use small molecules that disrupt the interaction between MYC and BPTF," according to Laia Richart, first author of the study, and to the rest of the authors in *Nature Communications*.

Looking For The 'Achilles Heel' In a Sea of Data

The strategy followed by the researchers requires collecting a huge amount of data (fishing expedition), of which only a fraction will be relevant. The ultimate goal of this type of approach is to identify, among the thousands of cellular errors that occur when a tumour develops, those that represent an Achilles heel for cancer cells.

"Sometimes you don't know whether you have caught a boot or a trout," says Real. Elucidating this—finding the relevant information among a jumble of data that are difficult to interpret—requires mass analysis tools, "intuition based on experience," and well-conducted experiments. This is an "absolutely necessary" strategy in current research projects, although it poses a real challenge for the researchers: "For several years, we were not sure about the relevance of BPTF in human cancer."

The results that are now being published in *Nature Communications* have required about seven years of work. The study has been co-directed by Paco Real and Víctor J. Sánchez-Arévalo, who also belongs to CNIO's Epithelial Carcinogenesis Group.

More information: Laia Richart et al. BPTF is required for c-MYC transcriptional activity and in vivo tumorigenesis, *Nature Communications* (2016). DOI: 10.1038/ncomms10153

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