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Valproic acid and rapamycin show potential anti tumour effect

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Two existing drugs valproic acid and rapamycin have the potential to play a role in the treatment of cancer by interfering with the DNA damage response mechanism, reports a study from the Istituto FIRC di Oncologia Molecolare (IFOM) and the Istituto Europeo di Oncologia (IEO) in *Nature*.

"There are two philosophies now in drug discovery. The first one is to discover new drugs from new targets, while the second option is to reposition existing drugs," says Marco Foiani, director of the cell cycle control and genome stability unit at the FIRC Institute of Molecular Oncology (Milan, Italy), who led the study, together with Saverio Minucci from IEO. "Our study takes advantage of an interesting strategy that combines the potential of genetic analysis conducted in simple biologic systems with analysis of the mechanism of action of drugs already in the clinic."

Valproic acid has been used for decades as an anti-epileptic; while rapamycin is used as an immunosuppressor in organ transplantation. The current study explored the effect of the two drugs in budding yeast cells and looked at the effect that they have on three processes that are known to be involved in tumour progression – the DNA damage response (where DNA lesions are repaired by different processes), protein acetylation (a protein regulation process) and autophagy (the ability of cells to self-destruct).

The first finding, which took the team five years, showed that treating the yeast cells with valproic acid, an inhibitor of protein deacetylation, switched off the signal for induction of the DNA damage response pathway (which saves the cell from genome damage). A second part of the study showed that treating the yeast cells with rapamycin (which triggers the autophagic response) had similar effects to valproic acid. The authors then connected the valproic acid and rapamycin effects: following valproic acid treatment, key proteins in the DNA damage response remain acetylated and are rapidly degraded by autophagy.

"Until now these processes have been thought to be distinct. What our study has shown is that they are tightly correlated and act synergistically to prevent cancer cell formation," explained Foiani, who believes that based on the results of these studies valproic acid and rapamycin-like drugs could have potent antitumour effects."The drugs seem to increase the ability of tumour cells to respond to DNA damage, and therefore could be used in combination with radiotherapy and radiomimetic drugs," added Foiani.

A recent study by David Harrison, published in Nature in July 2009, showed that treatment with rapamycin elongates the life span of mice. "We wouldn't be surprised if one of the reasons that the mice live longer is because rapamycin is limiting the DNA damage response," added Foiani.

Article: T Robert, F Vanoli, I Chiolo, et al. HDACs link DNA damage response, double strand breaking processing and autophagy. *Nature*. DOI: **10.1038/nature09803**