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CNIO researchers discover a new regulator of drug detoxication

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Drug abuse and alcohol are some of the most frequent causes of liver damage, particularly in developed countries. Such kind of liver damage can cause irreversible liver failure and even cancer. Researchers from the Spanish National Cancer Research Centre (CNIO) have discovered an important new protective role of the Fra-1 protein, which neutralizes the damage caused by agents, such as the analgesic drug acetaminophen (Paracetamol). This is the first study to reveal a function of Fra-1 in protecting this important organ. The study is published today in the journal *Hepatology*.

The journal includes a comment by David A. Brenner, from the University of California, who is a leader in the field of gastroenterological research, specializing in diseases of the liver. In the comment, Brenner highlights the importance of this study, saying that it "should provide new insights into the complex role of AP-1 [a family of proteins which Fra1 is part of] in liver disease and the potential role of inhibitors of the signalling pathway in the treatment of specific liver diseases."

A new 'super-detoxifying' mouse

Key to the study has been a new 'super-detoxifying' mouse model generated by the team around Erwin Wagner, Director of the BBVA Foundation-CNIO Cancer Cell Biology Programme and holder of an ERC Advanced Grant.

"Our mouse was designed to produce extra Fra-1 protein only in the liver, which allowed us to study its specific function in this organ and thus eliminate side effects that an excess of protein might have in other tissues", explains Sebastian Hasenfuss, first author of the study.

According to the article, increased production of Fra-1 in the liver of these mice protects the organ from damage caused by drugs, such as Paracetamol. Moreover, Erwin Wagner's team also found that the removal of Fra-1 in mice causes a significant increase in liver damage.

How Fra-1 protects the liver is another question that Wagner's team answers in the article. On one hand, Fra-1 stimulates genes related to the glutathione defence system against free radicals and thus avoids cellular damage. On the other hand, Fra-1 stimulates genes that cause the removal of toxins from the body.

These results bring to light a new molecular component that could be key in future studies searching for new drugs for diseases related to the accumulation of toxic compounds, such as acute liver disease, alcoholism or cancer.

The team also highlights the importance that Fra-1's detoxifying role might have in the generation of chemotherapy resistance: "Tumour cells use very similar mechanisms as Fra-1 to eliminate chemotherapeutic agents", says Wagner, concluding that: "This makes us think that tumours might use Fra-1 to generate chemotherapy resistance and thus be able to keep growing."

More information: The AP-1 transcription factor Fra-1 is dispensable for murine liver fibrosis, but modulates xenobiotic metabolism. Hasenfuss SC, Bakiri L, Thomsen MK, Hamacher R, Wagner EF. *Hepatology* (2013). DOI: 10.1002/hep.26518