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New aspects on the regulation of the methionine cycle in liver injury

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The methionine cycle produces S-adenosylmethionine (AdoMet) the main methyl donor for cellular transmethylation, including several epigenetic modifications. Alterations in this pathway and specifically in the AdoMet synthesis by methionine adenosyltransferases (MATs) have been reported in a large variety of diseases, although most studies have been performed in liver. The enzymes involved, excluding methyltransferases, are oligomers that were classically considered cytoplasmic. Thus, the AdoMet synthesized in the cytoplasm was expected to be transported to other compartments as required, a hypothesis further sustained by identification of an AdoMet mitochondrial transporter. However, in the last decade several reports have shown that this is not the case for the cell nucleus, where most of these enzymes have been identified in very low quantities. Work of my laboratory has recently provided evidence showing nuclear accumulation of several proteins of the methionine cycle in two models of acute liver injury. Moreover, we demonstrated that the nucleocytoplasmic distribution is governed by the ratio between glutathione species (GSH/GSSG). In fact, the oxidative stress induced by D-galactosamine or acetaminophen produces opposite effects on MAT I/III isoenzymes according to the subcellular compartment examined. This opposite regulation leads to decreased AdoMet production in the cytoplasm, whereas the nuclear levels of active MAT I increase, as well as certain epigenetic methylations. Prevention by N-acetylcysteine administration did not avoid all the drug-induced changes. Hence, we propose that alterations in the subcellular localization pattern of several enzymes of this cycle show a potential as biomarkers of liver disease.

Biography

María Ángeles Pajares completed her PhD from the Universidad Complutense de Madrid (Spain) in 1986, and her Post-doctoral studies from the Harvard Medical School (Boston, USA) in 1989. She is a Senior Research Scientist from the CSIC since 2006, where her own group works in the structure/function relationships that govern methionine metabolism in health and disease. She has authored more than 60 original papers in reputed international journals. She serves as referee for a large number of journals and several grant agencies and is now also serving as an Editorial Board Member for the *World Journal of Biological Chemistry*.

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