Nuclear shuttling of key methionine cycle enzymes in acute liver injury

Important metabolic enzymes have been classically ascribed to certain subcellular locations, where they perform their well-known function. In the last decades, several technological advances have allowed detection of these proteins in new locations, performing either their known catalytic role or a new function. This is the case of certain enzymes involved in the methionine cycle, such as betaine homocysteine S-methyltransferase (BHMT). This protein needs to associate into very stable tetramers in order to catalyze the transfer of a methyl group from betaine into homocysteine for the synthesis methionine, an otherwise essential amino acid. Classically, BHMT was defined as a very abundant liver protein in the cytoplasm of hepatocytes, but later some reports found the protein in tissues such as the eye lens or the cochlea. Our study now demonstrates that BHMT is expressed at low levels in a variety of tissues and that in many of them its preferred subcellular location is the nucleus.

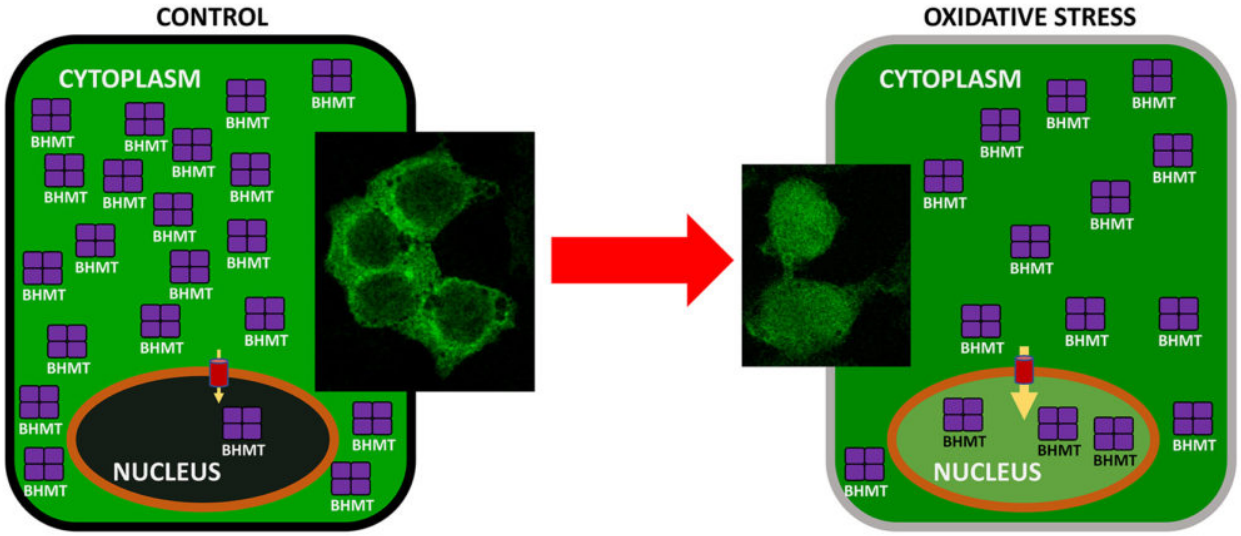

Fig. 1.

Hepatic nuclear BHMT is also an active tetramer able to synthesize methionine. Nevertheless, the nuclear BHMT content is markedly lower than in the cytoplasm of normal hepatocytes. Induction of acute liver injury with different agents (i.e. D-galactosamine or buthionine sulfoximine) changes the enzyme distribution between compartments and produces a certain level of oxidative stress. Precisely, BHMT content diminishes in the cytoplasm, while protein accumulation is observed in the nucleus. Unexpectedly, this change does not increase methionine synthesis in the nucleus, suggesting that the purpose of this shuttling may be linked to another protein function. In fact,

BHMT is involved in the control of osmolarity and its role as a structural protein in the eye lens has been proposed.

In acute liver injury, the failure to increase methionine synthesis by nuclear BHMT correlates with enhanced homocysteine levels in this compartment. Therefore, a larger number of nuclear proteins can become modified by homocysteine in a process named homocysteinylation. Such modification can be noxious for the cell by favoring the aggregation and inactivation of many proteins. Nuclear accumulation of BHMT can be precluded by agents that prevent the oxidative stress produced during acute liver injury. Surprisingly, the most common cause of human acute liver injury that is paracetamol intoxication does alter the subcellular distribution of BHMT. Paracetamol not only induces oxidative stress, but it is able to modify proteins. Therefore, it cannot be excluded that such a modification interferes with the transport mechanisms used for nuclear BHMT shuttling.

We also sought to identify the residues or signals that allow recognition of BHMT by the transporters that transfer the protein between cellular compartments. For this purpose, the sequence of the protein was analyzed in search of nuclear localization signals (NLS). No such signals were found, and hence the protein structure was examined to localize basic residues at the surface and to measure the distances among them. We found four basic residues at the BHMT's N-terminal that could arrange as a NLS and that are highly conserved. Mutation of these residues then showed that they are involved in the cytoplasmic retention of the enzyme.

Altogether results of the group demonstrate the existence of basic components of the hepatic methionine cycle both in the cytoplasm and the nucleus. Pathological oxidative stress induces shuttling of essential enzymes of the pathway to the nucleus in an attempt to increase the supply of metabolites for nuclear processes that are key for the regulation of gene expression. In this line, nuclear accumulation of BHMT reflects an effort to sustain methionine levels to support these processes, while keeping homocysteine concentrations under control. However, oxidative modifications on BHMT may hamper this desired result.

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