Enzymes that make and enzymes that fix mistakes: Nit1 is a ‘repair’ amidase that hydrolyzes deaminated glutathione

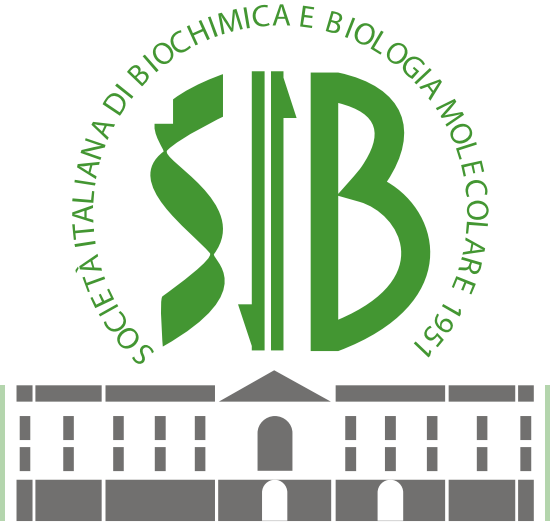
SIB 2017

59th CONGRESS

Italian Society of Biochemistry and Molecular Biology

Caserta, September 20 – 22, 2017

BOOK OF ABSTRACT



Enzymes that make and enzymes that fix mistakes: Nit1 is a 'repair' amidase that hydrolyzes deaminated glutathione

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Enzymes of intermediary metabolism are not perfectly specific and tend to act on intracellular compounds resembling their true substrate. The products of such side reactions are non-classical metabolites, which in several cases need to be eliminated or recycled by specific enzymes, called metabolite repair enzymes [1, 2]. The increasing rate at which repair enzymes are being discovered suggests that a substantial fraction of currently 'unclassified' enzymes, encoded in eukaryotic and prokaryotic genomes, might in fact be involved in metabolite repair.

Here I will describe a study on the mammalian protein Nit1, whose enzymatic function has long remained a puzzle. Nit1 is highly conserved in eukaryotes and is thought to act as tumor suppressor. Despite being ~35% sequence identical to ω-amidase (Nit2), it had been shown that Nit1 does not hydrolyze efficiently α-ketoglutaramate (the known physiological substrate of Nit2).

However, we demonstrated that both the mammalian Nit1 and its yeast ortholog can very efficiently hydrolize deaminated glutathione (dGSH), i.e., a form of glutathione in which the free amino group has been replaced by a carbonyl group. We further showed that *Nit1*-KO mutants of both human and yeast cells accumulate dGSH, and that the same compound is excreted in large amounts in the urine of *Nit1*-KO mice. Finally, we showed that several mammalian aminotransferases can form dGSH *via* a common (if slow) side-reaction, and provided indirect evidence that transaminases are mainly responsible for dGSH formation in cultured mammalian cells.

Altogether, these findings delineate a typical instance of metabolite repair, whereby the promiscuous activity of some abundant enzyme(s) of primary metabolism leads to the formation of a useless and

potentially harmful compound, which needs a suitable 'repair' enzyme to be destroyed or reconverted into a useful metabolite. The need for a dGSH repair reaction does not seem limited to eukaryotes: we demonstrated that Nit1 homologs acting as excellent dGSH amidases also occur in *Escherichia coli* and other glutathione-producing bacteria [3].

References

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