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Letter to the Editor

Gamma-glutamyltransferase, H_2O_2-induced apoptosis and expression of catalase

Dear Editor:

We would like to call the attention of the readers on a biochemical aspect generating occasional disputes in studies concerned with oxidative stress-related apoptosis. The paper recently published in this journal by Moon et al. (2012) documents that the mutation of K-RAS in prostate epithelial cells causes the activation of the ERK signalling pathway and an increased expression of gamma-glutamyltransferase-2 (GGT2). This was accompanied by a reduction in cellular production of reactive oxygen species (ROS) as well as by induction of resistance to H_2O_2-induced cell death. As GGT2 enzyme activity is known to contribute to maintenance of cellular homeostasis of glutathione (GSH), the authors conclude that the observed resistance to H_2O_2 is likely the result of increased intracellular levels of this major antioxidant. GSH levels in control and K-RAS-mutated cells were however not determined.

Our laboratory has repeatedly reported on the antiapoptotic effects of GGT expression, but a relationship with increased cellular GSH levels could never be confirmed (Del Bello et al., 1999; Franzini et al., 2006; Giommarelli et al., 2008). On the contrary, these studies highlighted how GGT expression actually results in a *decrease* of cellular GSH levels, likely due to the (often overlooked) prooxidant role of this enzyme activity. Indeed, an apparent 'GSH oxidase' activity of GGT was described since earlier studies (Tate et al., 1979), and more recently it was shown that generation of prooxidant species, including H_2O_2 itself, can occur during GGT activity following the interaction of the GSH metabolite cysteinyl-glycine with redox-active transition metals, notably iron (Dominici et al., 1999).

The prooxidant effects of GGT activity were shown to produce significant changes in the cell redox status, exerting modulatory effects on several molecular targets in signal transduction pathways (reviewed in Dominici et al. (2005)). With regard to apoptosis, we have shown that the increased resistance of GGT-expressing cells to H_2O_2-induced apoptosis is not related to intracellular GSH content, but rather results from activation of ASK-1/p38 signalling and increased expression of cellular catalase, resulting in decreased ROS formation and protection against ROS-induced DNA damage (Giommarelli et al., 2008, 2009). Interestingly, besides the phenomena described by Moon et al. in K-RAS transformed cells, the described mechanisms likely account for the resistance of GGT-expressing cells to apoptosis induced by cytotoxic agents (Giommarelli et al., 2009; Corti et al., 2010). Altogether, the functions played by GGT activity in cellular homeostasis may be more complex than traditionally appreciated, and caution should be put in interpreting the effects of GGT expression solely in terms of cellular GSH supply.

Conflict of interest statement

None declared.

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Alfonso Pompella *
Aldo Paolicchi
Alessandro Corti
Dept. of Experimental Pathology,
University of Pisa Medical School,
Via Roma 55, 56126 Pisa, Italy
* *Tel.: +39 050 2218 537; fax: +39 050 2218 557.*
E-mail address: alfonso.pompella@med.unipi.it (A. Pompella)

Maria Franzini
Scuola Superiore S. Anna di Studi Universitari e di Perfezionamento,
Piazza Martiri della Libertà 33,
56127 Pisa, Italy

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