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Antioxidant mechanisms of ellagic acid with special focussing on metallothionein

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The study revealed the pivotal role of ellagic acid (EA) in different cellular antioxidant mechanisms and defense lines. The role of EA is much more complicated than other known antioxidants, since it interacts with divers mechanisms with different roles. *In vitro* experiments indicated that EA has high scavenging activity against physiological reactive species ($ROO^{\bullet}$, $OH^{\bullet}$, Cu^{2+} and $O_2^{\bullet-}$). I*n vivo* experiments confirmed that EA enhanced significantly the antioxidant activities of both the protein and non-protein fractions of HUH-7 cells against $ROO^{\bullet}$ and $OH^{\bullet}$. Our results demonstrated that the protein antioxidants are mostly responsible of the antioxidant activity of control cells. EA strongly enhanced the activity of catalase, glutathione peroxidase, and thioredoxin reductase in HUH-7 cells, which explain the induced total cellular antioxidant activity against ROS after EA treatment. EA cell treatment significantly induced total thiol and glutathione levels, and enhanced metallothionein (MT) protein biosynthesis. EA selectively up-regulated of *h*MT-1a and down-regulated of *h*MT-2a mRNA expression. EA enhanced the MTF-1 binding activity to MRE-a and MRE-c consensus sequences and inhibit MTF-1 affinity towards MRE-b. This may be due to the competitive binding activity of Sp1 with MTF-1 to MRE-b and to the competitive affinities of other MREs, Sp-1 and AP-2α to be bound by transcription factors. In addition, EA induced the protein binding activity to the Sp1 consensus sequence and inhibited the affinity to the AP-2 α motif without any influence on AP-1. The induction of hMT-1a expression and the inhibition of *h*MT-2a expression may be a net result of the concomitant induction and inhibition of the binding activities of the transcription factors (MTF-1 and Sp1) to different *cis*-acting elements in the MT promoter region (MRE-a-d, Sp1, AP-1 and AP-2 α).EA plays an important role in protein sulfhydryl repair mechanisms, in protection from the oxidative stress-induced cell damage via inhibition of single strand break formation, reduction of intracellular calcium, and inhibition of lipid peroxidation. It is known that most of EA was rapidly absorbed after 2 hours of oral administration and 41% of EA was excreted in faeces and urine, in either free or conjugated–metabolite forms after 24 h of the intake. Therefore, EA represents a natural way to eliminate the free radicals from the human body, besides its overall potential induction to several antioxidants mechanisms. EA may provide a natural source to detoxify liver carcinogens, especially free radicals, which are one of the major etiological factors of hepatocellular carcinoma (HCC), thereby EA can help in prevention from HCC.