LETTER TO THE EDITOR

Redox-regulated mechanism may account for zerumbone’s ability to suppress cancer-cell proliferation.

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A recent report shows that zerumbone (ZER) inhibits the proliferation of, and induces apoptosis in, colon cancer cells. We suggest a mechanism for these phenomena, based on our recently proposed redox model of cell proliferation which stresses the importance of intracellular redox potential $E$ in the control of proliferation of normal and cancer cells.

Murakami et al. (1) recently reported that zerumbone (ZER) inhibits the proliferation of colon cancer cells and induces apoptosis in them, while having less effect on normal-cell proliferation. Their study pointed to the α,β-unsaturated carbonyl group in ZER as the likely source of the effect. They called this finding ‘intriguing’ and suggested that this group may play an important role in unknown reactions with unidentified target molecule(s).

We also find their results intriguing, because they corroborate our recently proposed redox model of cell proliferation (2). The model is based on a newly discovered role of the intracellular redox potential $E$ as an important factor in the control of proliferation of normal cells. $E$ is proportional to the logarithm of $\frac{[\text{GSSG}]}{[\text{GSH}]}^2$, where $[\text{GSSG}]$ and $[\text{GSH}]$, respectively, are the oxidized and reduced forms of glutathione. The α,β-unsaturated carbonyl group effectively removes the intracellular GSH by forming a Michael adduct with it, thereby raising $E$, which in turn stops the proliferation of the cancer cells.

According to our model, if $E$ is above an appropriate threshold value $\theta$, the RB protein cannot become, or even remain, phosphorylated. It is well known that the RB protein acts as a brake on the cell cycle. When phosphorylated, it permits the cell to pass the restriction point, $R$. Unless RB becomes phosphorylated, a proliferating cell will stop cycling in mid-G₁, before $R$ and this arrested cell may then undergo apoptosis.

When Murakami et al. (1) administered ZER to the cancer cells, the α,β-unsaturated carbonyl group on the ZER (partially) depleted the GSH in the cell, bringing $E$ above $\theta$, dephosphorylating RB and stopping the cell cycle.

Our model also accounts for the weaker effect of ZER on the proliferation of normal cells. Hutter et al. (3) found that the average $E$ in proliferating fibroblasts is about $-220$ mV, and that in proliferating fibrosarcoma cells it is about $-210$ mV. We have induced the threshold value of $\theta$ to be about $-205$ mV. There is thus a margin of ~10 mV in the adjustability of $E$ between these normal cells and the cancer cells. It is thus possible that with an appropriate dose of ZER, $E$ can be made high enough to stop the proliferation of cancer cells, but not high enough to stop the proliferation of normal cells.

References


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