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D-galactose might protect against ionizing radiation by stimulating oxidative metabolism and modulating redox homeostasis

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Dear Editor,

We read with great interest a recent study by Zhu *et al.* [1], which suggests that repeated parenteral administration of D-galactose (750 mg/kg/day) exerts protective effects against ionizing radiation-induced injury in mice possibly by modulating gut microbiota. This letter intends to supplement the aforementioned article by proposing an additional mechanism of action that may explain the protective effects of D-galactose pretreatment against ionizing radiation-induced injury.

We first wish to emphasize that the work by Zhu *et al.* [1] presents several observations that provide invaluable information for elucidating the mechanisms responsible for the biological effects of D-galactose. A detailed explanation of the importance of each finding in the context of research on the biological effects of D-galactose is beyond the scope of this letter; however, two somewhat unexpected findings have to be acknowledged. Firstly, Zhu *et al.* demonstrated for the first time that treatment with high dose of D-galactose (750 mg/kg/day) is not necessarily associated with detrimental health effects (in contrast, it surprisingly provided protection against ionizing radiation-induced injury). The exact plasma concentration of D-galactose was not reported by Zhu *et al.*; however, ∼80% of studies achieve high plasma concentrations using as little as <300 mg/kg of D-galactose per day to induce an aging-like phenotype [2] - therefore, it is reasonable to assume very high plasma concentrations with 750 mg/kg/day (as used by Zhu *et al.*). Secondly, D-galactose has the potential to exert beneficial effects by modulating gut microbiota, not only after peroral but also following parenteral administration.

Current research provides strong evidence that most reported beneficial and harmful effects of D-galactose in rodents can be explained by tissue exposure, with dose and route of administration being the two most important determinants [3]. In general, exposure to low concentrations of D-galactose has so far been associated with beneficial health effects. The exposure to low concentrations of D-galactose has been achieved by (i) administration via the oral route (e.g. D-galactose dissolved in drinking water available *ad libitum*) due to the buffering capacity of gastrointestinal absorption and liver retention of ∼88% of orally administered D-galactose [4, 5–7]; (ii) parenteral administration of low doses of D-galactose [8]. In contrast, the exposure to high concentrations of D-galactose by parenteral [2] or bolus oral administration [9, 10] (e.g. see Knezovic *et al.* [7]) has been shown to induce detrimental effects. Taking into account that Zhu *et al.* repeatedly administered a large dose of D-galactose (750 mg/kg/day) via the parenteral route, the reported results provide for the first time evidence that high tissue D-galactose exposure has the potential to exert beneficial health effects. It has to be taken into account that it is still not clear whether and to what degree the effects of D-galactose depend on the underlying pathophysiology. For example, although chronic oral D-galactose treatment was associated with improved cognitive function in the streptozotocin-induced rat model of Alzheimer's disease (+400% latency time in the passive avoidance test; +44% time in the target quadrant in the Morris water maze test), a slight reduction in cognitive performance was observed in D-galactose-treated controls (−15% latency time in the passive avoidance test; −20% time in the target quadrant in the Morris water maze test) [7].

Furthermore, Zhu *et al.* [1] provide the first evidence that D-galactose treatment-induced favorable modulation of gut microbiota does not depend on the oral route of administration. The results of Kim *et al.* [5] show that oral administration of D-galactose may exert beneficial effects by modulating gut microbiota—e.g. by decreasing the *Firmicutes* to *Bacteroidetes* abundance ratio. Zhu *et al.* [1] provide convincing data demonstrating that the observed beneficial effects

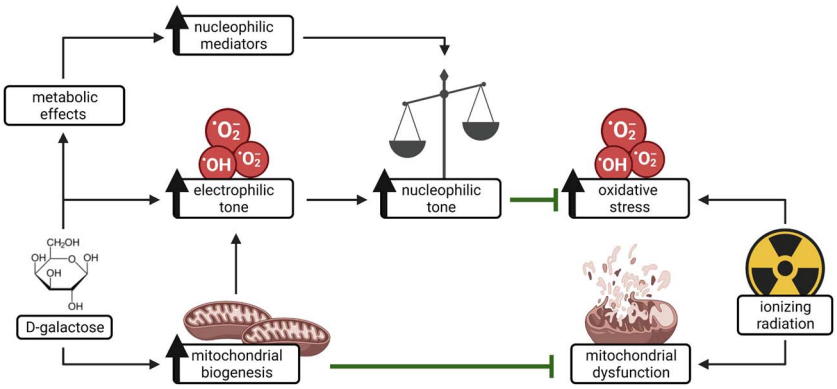

Fig. 1. Proposed mechanisms mediating protective effects of D-galactose against ionizing radiation.

of D-galactose in their study were at least partially mediated by gut microbiota, as fecal transplantation from the D-galactose donor mice provided protection from ionizing radiation. The gut microbiome can be modulated by a myriad of factors and it is possible that oral and parenteral D-galactose modulate gut microbiome by different mechanisms; however, the findings reported by Zhu *et al.* clearly demonstrate that, somewhat unexpectedly, even parenteral D-galactose has the potential to favorably influence the intraluminal environment and gut microbiota.

Considering that fecal transplantation provided only partial protection against ionizing radiation-induced injury (~50% of D-galactose-treated mice vs ~30% of fecal transplantation-treated mice survive in the first 30 days after 7.5 Gy total body irradiation), it is possible that favorable modulation of gut microbiota may not be the main mediator of the observed protective effects of D-galactose [1]. We propose that the observed protection against irradiation provided by D-galactose pretreatment may at least partially be mediated by enhanced oxidative metabolism [11] and hormetic modulation of redox homeostasis with increased capacity to tolerate oxidative stress [3, 12].

D-galactose is widely utilized in metabolic studies due to its ability to promote oxidative metabolism and reverse the Warburg effect. Although the production of pyruvate from glucose in the glycolytic pathway yields a net gain of two molecules of adenosine triphosphate (ATP), no ATP is generated in the process of glycolytic conversion of galactose, so in the presence of D-galactose, cells rely on oxidative phosphorylation (OXPHOS) to maintain energy homeostasis [11]. Nevertheless, the inability to generate ATP in the glycolytic pathway does not seem to be the only mechanism by which D-galactose promotes oxidative metabolism, as it has been shown that transient galactose exposure has the potential to promote cellular uptake and oxidative metabolism of glucose [13]. Furthermore, exposure to D-galactose alters the mitochondrial structure and increases the expression and activity of mitochondrial enzymes [14]. The ability of D-galactose to promote oxidative metabolism could provide some protection against ionizing radiation-induced injury in at least two ways: (i) stimulation of mitochondrial number and metabolic capacity; and (ii) hormetic stimulation of nucleophilic tone.

The effects of ionizing radiation on mitochondria have been summarized elsewhere (e.g. see literature [15, 16]). *In vivo* and *in vitro* studies have consistently shown that ionizing radiation reduces the activity of the electron transport chain enzymes and inhibits OXPHOS resulting in a diminished ability to generate ATP [15]. In the context of the study by Zhu *et al.* [1], 7-day D-galactose pretreatment could have stimulated mitochondrial biogenesis and increased the expression and the activity of mitochondrial enzymes resulting in increased functional mitochondrial capacity.

Furthermore, D-galactose-induced potentiation of OXPHOS results in increased generation of free radicals (major byproducts of oxidative metabolism), which provides a hormetic stimulus for upregulation of the nucleophilic tone to maintain the redox rheostat setpoint [17]. In addition, D-galactose has the ability to disinhibit the oxidative pentose phosphate pathway flux [12, 18] with the potential to replenish cellular reductive equivalents critical for the maintenance of the nucleophilic tone (particularly during the electrophilic challenge such as the one caused by oxidative metabolism potentiation) [17]. Taken together, D-galactose has the potential to increase the cellular capacity for tolerating oxidative stress [3, 12]. Considering that oxidative stress has been proposed as a major mechanism mediating pathophysiological effects of ionizing radiation [19, 20], the potential of D-galactose to (i) precondition the cells to oxidative challenge (by increasing the baseline production of free radicals); and (ii) reroute metabolism towards increased production of nucleophilic mediators (increasing the resilience of the redox system to perturbations by exogenous stimuli) could have had a major impact on the resilience to ionizing radiation-induced injury observed by Zhu *et al.* [1] (Fig. 1).

In summary, the study by Zhu *et al.* [1] provides important information for elucidating the biological effects of D-galactose and demonstrates its promising potential for protection against ionizing radiation. Considering the important effects of D-galactose on oxidative metabolism and redox homeostasis, future research should elucidate whether the observed effects might have been mediated by the ability of galactose to promote mitochondrial function and biogenesis and increase the capacity of cells for tolerating oxidative stress.

CONFLICT OF INTEREST

None.

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DATA AVAILABILITY

Not applicable.

AUTHOR'S CONTRIBUTIONS

J.H. wrote the letter. A.B.P., D.V., A.K., J.O.B. and M.S.P. provided critical feedback on the manuscript. All authors provided final approval of the version to be published.

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