Editorial

Potential use of dietary antioxidant to prevent radiation-induced genomic instability

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Abbreviations: ROS, reactive oxygen species; DDR, dna damage response; GT3, gamma tocotrienol; HMGCR, hydroxyl-methyl-glutaryl-coenzyme reductase; TM, thrombomodulin; APC, activated protein c

Editorial

Exposure to radiation is inevitable in our lifetime whether from natural, diagnostic and/ or therapeutic sources. Moreover, the peril of radiological accidents and the threat from radiological terrorism have posed a serious security issue for military personnel and civilians as well. Radiation can cause serious damage to various cellular components based on radiation dose, dose-rate, quality, tissue type and inter-individual variability of radiation sensitivity. The damaged cells may result in subsequent adverse health issues. Among the radiation-induced insults to various cellular organelles, breakages to nuclear DNA is the most critical factor that determines the fate of irradiated cells and is depending on the extent and quality of DNA breaks.

Irradiation induces DNA strand breaks within milliseconds of exposure. Cellular DNA repair machineries immediately sense and locate the broken parts of DNA and activate a variety of DNA repair path ways to restore normal genetic makeup after radiation damage. During this active process of DNA repair, broken strands may improperly rejoin in some of the irradiated cells and are propagated through cell generations. These cells, with altered genetic composition, may eventually result in path physiological conditions. This phenomenon of development of delayed genetic alterations is widely known as genomic instability. Genomic instability is associated with the progression and development of plethora of diseases including cancer, hematological, neurological and cardiovascular disorders.[1,2] However, the mechanistic link between radiation-induced DNA breaks and subsequent development of genomic instability has not been clearly elucidated.

A recent study has demonstrated that damage to DNA by radiation mimetic agent activates DNA Damage Response (DDR) cascade, which in turn induces ROS generation through the H2AX-Nox1/Rac1 pathway; while treatment with antioxidants suppress ROS generation and DDR activation, thus restricts DNA damage and also promotes cell viability.[3] These data clearly indicate that antioxidants play critical role in suppressing DNA damage by blocking excess ROS production after oxidative stress. Vitamin E analog gamma tocotrienol (GT3) is a potent radio-protector and is the natural compound with the largest dose reduction factor discovered to date.[4] GT3 provides considerable post-irradiation protection to hematopoietic and gastrointestinal system in mice.[5] GT3 also attenuates radiation-induced aortal peroxynitrite formation, hematopoietic stem cells depletion and helps in mobilization of bone marrow progenitor cells into peripheral blood after total body irradiation in mice.[5,6] However, the mechanisms underlying GT3-mediated alleviation of adverse radiation effects are not completely understood.

GT3, by virtue of its superior antioxidant properties, effectively prevents stress-induced lipid peroxidation, ROS production and heat shock protein expression. Moreover, GT3 has ability to inhibit the enzyme hydroxyl-methyl-glutaryl-coenzyme A reductase (HMGCR), similar to the lipid lowering drugs statins. Inhibition of HMGCR has been shown to protect mice from radiation-induced lung and vascular endothelium injury.[5] *In vivo* studies have demonstrated that a strong correlation exist between HMGCR activation and ROS production.[7] In addition, inhibition of HMGCR up-regulates endothelial thrombomodulin (TM) expression. Enhanced TM expression, in turn, stimulates activated protein C (APC) generation via forming a complex with thrombin. APC has been shown to have antioxidant property and limits stress-induced ROS production, lipid peroxidation and advanced glycation end products formation.[8] We have recently demonstrated GT3, like statins, up-regulates TM expression and APC generation; and GT3-mediated radiation lethality protection is TM-dependent.[9] Moreover, previous study has proved that systemic administration of recombinant TM and APC rescued mice lethal dose of radiation. APC is also known to have anti-inflammatory property, which plays critical role to maintain cellular redox homeostasis.[10] Finally, GT3 is a potent inducer of G-CSF, which mobilizes stem cells and also suppresses oxidative stress-induced surplus ROS production and lipid peroxidation.[11] All of these effects undoubtedly suggest that GT3 has robust antioxidant functions, which could play a critical role in attenuating radiation-induced DNA damage and therefore, would be a good candidate to prevent radiation-induced genomic instability (Figure 1).

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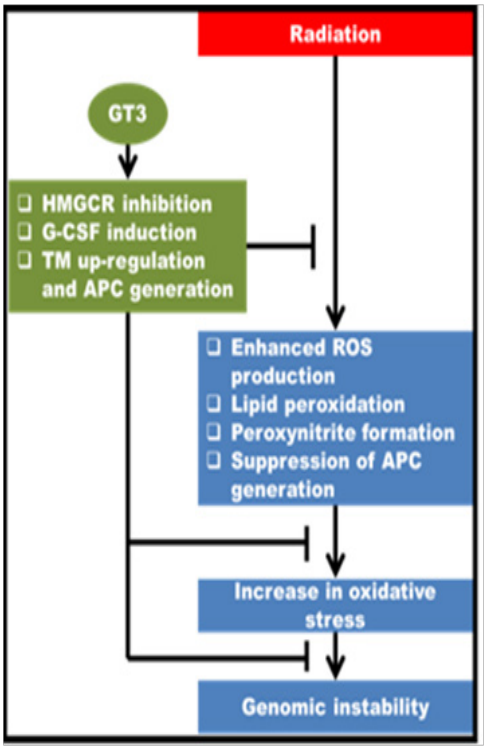

Figure 1 Schematic representation of possible mechanisms of GT3-mediated suppression of radiation-induced genomic instability.

Conflict of interest

The author declares no conflict of interest.

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