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Editorial

Does the Self-Regenerated Persulfide Fuel Tumor Progression through Bypassing Ferroptosis??

Md. Morshedul Alam[1,2]*

[1]*Department of Genetic Engineering and Biotechnology, Bangabandhu Sheikh Mujibur Rahman Maritime University, Mirpur, Dhaka, Bangladesh*

[2]*Department of Gene Expression Regulation, Institute of Development, Aging, and Cancer (IDAC), Tohoku University, Sendai, Japan*

***Corresponding Author:** Md. Morshedul Alam, Department of Genetic Engineering and Biotechnology, Bangabandhu Sheikh Mujibur Rahman Maritime University, Mirpur, Dhaka, Bangladesh.

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Abstract

Now a day, many scientists working on aging, are focusing on polysulfide metabolism and sulfur respiration research in coordination with anti-aging phenotypes. Several studies suggests that sulfur respiration is good for health with specific emphasis on healthy aging as polysulfide or hydropersulfide species are activating the autophagy pathway, and also possessing anti-inflammatory activity, regulation of mitochondrial metabolism and so on. Recent studies also suggest hydropersulfide as a super radical scavenger, but the precise molecular mechanism has yet to be unveiled. Very recent finding of Barayeu U. *et al.* suggested that hydropersulfide has auto-recycling capacity and after generating recycled hydropersulfide, it becomes inert/inactive until it gets favorable reaction environment in the next. Under these circumstance, very minute amount of exogenous supplementation of sulfane sulfur molecule can activate the hydropresulfide-mediated radical scavenging by utilizing the inert hydropersulfide or recycled hydropersulfide that works a as super radical scavenger than some other radical scavenger, such as N-acetyl cysteine (NAC). Barayeu U., *et al*. also suggested that by this alternative function, hydropersulfide also bypasses the ferroptosis-mediated cell death and support cellular longevity that could be a deteriorating approach for cancer metastasis. This study also gives a clue about how stressed tumor cells escape cellular death.

Keywords: *Hydropersulfide; Ferroptosis; Radical Scavenger; Longevity; Cancer*

The fundamental units of all living things are cells. The fundamental prerequisite of life is healthy cellular growth and metabolism. For healthy cellular metabolism and postponed aging, a normal homeostatic metabolism is essential. Cells of a living organism respond differently to its environment, and as a result, they modify their metabolic processes to adapt to the harsh conditions that cause aging phenotypes including diabetes, cancer, and numerous neurological illnesses. In order to scavenge the reactive oxygen species (ROS) or lipid peroxides produced by oxidative stress and the harsh environment of oxidative stress, cells attempt to strengthen their antioxidative system [1-3]. Cells can tolerate the redox stress up to a certain level with the support of antioxidant defense response such as KEAP1-NRF2 system, but when it goes to the threshold level of cellular tolerance level, it leads to DNA damage or genomic instability and therefore cancer or tumor manifestations are observed [4].

By scavenging (ROS), boosting autophagy, speeding apoptosis, increasing mitophagy, and decreasing lipid peroxidation (LPO), an activated antioxidant defense system can halt the growth of cancer cells in the early stages. According to growing evidence [5-7], the last two

traits are frequently governed by cellular sulfur metabolism. The ability of cells to generate large amounts of persulfides from the sulfur-containing amino acid cysteine has recently come to light. For scientists, the function of this particle in biology is still a myth. According to several studies, cells produce glutathione when they have a lot of cysteine, which boosts their antioxidant defenses. They also activate a protein called cysteine dependent-GPX4 to prevent ferroptotic cell death and reduce lipid peroxidation [8]. Cellular sulfur supports antioxidant, thiomethylation, and anti-inflammatory activities via supporting sulfur metabolism, which is also necessary for mitochondrial membrane potential and ATP synthesis [5].

Due to its higher susceptibility, ferroptosis, also known as the iron-based cell death system, is currently regarded as one of the main pathways of cancer chemotherapy. The question of why many cancer cells avoid the ferroptosis-dependent cell destiny arises, and it is important to look into any potential escape routes. It is well known that persulfides react with radicals much more powerfully than other types of radical scavengers. Recent research has shown that cells exposed to radicals and at danger of ferroptotic cell death exhibit increased persulfide production, which is a definite sign of persulfide-based cellular survival [9]. Researchers showed that persulfides can suppress ferroptosis and can also interfere the destructive chain reaction to protect cell membrane integrity. Since persulfide-based radical scavenging goes through a chain reaction, it is demonstrated in a recent finding that encountering a radical, persulfide itself becomes an inert radical that incapable to damage cells. It can react with itself and produce persulfide again in a subsequent chain reaction. So that unlike other radical scavengers persulfides are mostly consumed to eliminate oxidants/radicals [9]. Therefore, a huge surprise in sulfur metabolism and the development of cancer cells that have eluded ferroptosis is that extremely small amounts or low concentrations of persulfide can effectively quench a higher concentration of radicals.

Persulfides are well known for their health benefits, particularly in aging research. Further, in-depth research is required to determine how persulfide-based cellular mechanisms can be used in cancer chemoprevention.

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