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Caspase-1/Interleukin-1 (an Eminent Inhibitor): Can be a Future Radioprotector?

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Abstract

Cancer is a multifaceted disease, multiplies unmanageably and spread among the human body severely through the metastasis process. To address this challenging issue and to diminish progressive cancerous cells, high doses of radiation are implemented in radiotherapy. However, enormous cell death and potential impairment eventuated to tissues upon acute radiation exposure, resulting in the destruction of double-stranded DNA and inevitably death. Radioprotectors plays a pivotal role in the curation process of tumor in radiotherapy. In our opinion, due to the vital role of caspase-1 in the inflammatory immune response, it can serve as a function of a radioprotector. From a broader perspective, it may open a new window for researchers to discover novel therapeutic approaches to enhance human health. At the same time, it will be a crucial step to understand and unravel the controversial mechanism of action of caspase-1 and inflammation which may help to curb tumors with cancer patients in the near future.

Abbreviations: RNS: Reactive Nitrogen Species; ROS: Reactive Oxygen Species; IR: Ionizing Radiation; FDA: Food and Drug Administration

Introduction

In the advancement of science, the employment of contemporary radiation therapy (xRT); the most effective way to counter malignancy, in the realm of cancer treatment has been exploited in the last few decades extensively. Although, half of all cancer patients worldwide, treated by radiotherapy may be responsible for the consequential damage to healthy normal cells and acute injuries to tissues which remains an enormous challenge to the radiotherapist and oncologist [1]. On the other hand, tremendous research which involves; novel drug development and innovative strategies are in the phase of progress and is constantly evolving across the globe to help reduce radiation-induced multiple side-effects. As massive doses of radiation are implemented as a part of radiotherapy to cease the progress of cancerous cells, but at the same time, it is harming enormously to the healthier normal cells. The risk of damaging normal cells can be accomplished by practicing an accurate and improved localization of radiation dose and with the aid of several radioprotectors [2].

The most frequently applied techniques in anticancer treatment include Ionizing radiation (IR), in particular X-rays and gamma-rays owing to their huge potential to penetrate tissues; subsequently rupture chemical bonds resulted in free electrons from atoms which ionized, ultimately destroy the tumor cells. The water molecules existent in the human organisms spontaneously (within a few milliseconds) break down into active oxygen by radiation; eventually, engender free radicals, Reactive Oxygen Species (ROS), and Reactive Nitrogen Species (RNS) [3], which subsequently impair cells and in extreme cases leads to death. The generated free radicals' interplay with DNA, RNA, proteins and resulted in cell dysfunction and further fatality. Also, these active free radicals induce oxidative stress among healthy organisms in physiological

and pathological processes, which is one of the causative factors for tumors, hence, therefore, further exploration and the investigation of a powerful free radical scavenger is urgently needed.

The fundamental goal of radiotherapy is to help destroy cancerous cells specifically without or negligible harm to the normal healthier cells and tissues. This process can be accomplished either by irradiation at tumor cells particularly or by employing various radioprotecting agents to minimize the risk [4]. The one of the best key model to downplay the risk of damaging cells is to eradicate free radicals which produced in due course of radiotherapy from the human body. In the broader sense, primarily it causes DNA double-strand rupture during irradiation. Many researchers around the world are thus, formulating diverse radiosensitizing agents and radioprotectors as a protective agent that can shield the human body in radiotherapy to curb adverse effects. In our opinion caspase-1, an eminent inhibitor that interplays a critical role in radiation-induced apoptosis can become an additional option as a radioprotector and will open new windows of opportunities in the application domain of radiotherapy.

Radioprotectors

Radioprotectors are compounds that are introduced before or at the time of radiation to diminish impairment occurred during acute radiation exposure in the treatment against cancer. At the same time, radioprotectors, facilitate to restraint of the worsening of normal healthy cells in the process of radiotherapy in many regards. To date, Amifostine (WR-2721) which is the only U.S. Food and Drug Administration (FDA) permitted radioprotector; mechanistically scavenges the highly reactive free radicals generated by ionizing radiation in radiotherapy. However, only a high concentration dose is beneficial in radiotherapy which also decayed within 30 minutes. Additionally, it may cause adverse side-reactions for example vomiting, nausea, diarrhea, neurotoxicity, sneezing, and, dizziness, etc. [5]. Nitroxides, the most promising future radioprotector capable to detoxify ROS; still under the pathway of clinical trials. Other antioxidants, the naturally occurring radioprotectors, including glutathione, lipoic acid, vitamins A, C, and E have less efficacy and non-selective free radical scavenging ability in comparison with the synthetic agents.

Their mode of action includes detoxification of ROS, tyrosine kinase inhibitor and, hematopoietic stem cell quiescence. Superoxide dismutase (SOD), an enzyme that naturally exists in human cells; which catalyzes and detoxifies the highly reactive superoxide to oxygen (O_2) and hydrogen peroxide(H_2O_2), free radicals generated upon radiation exposure [6]. Furthermore, Cytokines and growth factors also play a role of radioprotector, serve to stimulates proliferation and differentiation, DNA repair and ROS detoxification. ACE inhibitors operate through the mechanism of angiotensin II inhibition, suppression of radiation-induced proliferation, NOS synthesis and, TGF-β induction. In addition, many other nano-particle-based, novel radioprotectors are in the progressive stages with a diverse application, mode of action, and their relevant side effects. The aforementioned limitations impart massive challenges in front of researchers to discover effective radioprotectors.

Caspase-1

The neuronal cell death emerges via two main pathways-extrinsic (death receptors) and intrinsic (mitochondria). Among these, the caspase follows the mitochondrial pathway after exposure to acute radiation. The caspases, conduct a pivotal role in complex physiopathological processes to regulate apoptosis and which also contribute to inhibiting radiation-induced apoptosis [7]. The intracellular cysteine proteases family includes the inflammasomes caspases which are solemnly responsible to split an insignificant number of substrates exhibits succeeding aspartic acid residues [8]. To date, extensive research has been performed to understand the significant role of caspases in the complex biological process of apoptosis. This caspases family is mainly categorized into inflammatory mediated caspases (caspase-1, 4, 5, 11, and 12) and apoptotic (caspase-2, 3, 6, 7, 8, 9, and 10). Amid diverse caspase families, inclusive of human caspase-1, caspase-4, and caspase-5 and other mouse caspase-1, caspase-11, and caspase-12, are well-known 'proinflammatory caspases' as specifically, they are frequently participating in the biological processes and secretion of proinflammatory molecules.

Among those, Caspase-1 is first discovered in 1989 and then consistently studied and well-characterized in 1992 [9,10]. As one of the most significant and systematically investigated caspase-1(inflammatory mediated) which triggers the inflammatory response process via the stimulation of pro-inflammatory cytokines, in particular, interleukin-1β (IL-1β) and IL- 18 as well as the pyroptosis [11]. After maturation, the cytokines subsequently start signaling events to stimulate a pro-inflammatory response; its corresponding swiftness, selectivity, and sort of reply are subject to the signal received together with the sensor protein which receives signals. Thus, an activated Caspase-1 can provoke pyroptosis (a lytic form of cell death) reliant on the signal received. However inflammatory response can occur with or without pyroptosis, but prior pyroptosis process, the inflammatory response is fully necessary [12].

However, the precise mechanisms underlying this pathology remain unraveled. It is renowned fact that inflammation is an important pathway in the host defense system. Inflammasomes are associated with acute danger or pathogen-related inflammation; besides, they engaged in the growth of inflammation-induced

illnesses, for instance, cancer and many others. Pyroptosis which is a lytic form of programmed cell death is mainly governed by caspase-1 and triggers IL-1- or IL-18 related inflammatory response. Regulating diverse and moderately opposing pathways, caspase-1 assist innate and adaptive immunologic defense mechanisms. Experimentally, it was proven that caspase-1 helps cell survival by activating NF-kB, triggers membrane repair, and controls the eccentric discharge of certain proteins [13]. As undesirable adverse effects occur during the course of radiation therapy, which also involves cell and tissue damages.

Considering the aforementioned facts in mind, in our viewpoint, owing to its central role in the inflammatory immune response, caspase-1 which triggers the inflammatory response by activation; may play a promising role in the inflammation that occurs during radiation. Thus, caspase-1 may become a new therapeutic target for irradiation in cancer treatment. In this regard, critical mechanisms of inflammatory caspase-1 and its radioprotecting ability have to be investigated in detail.

Conclusion

This review summarizes the interplay of radiation and its critical role in the curation of tumors and how it damaging healthier normal cells in conjugation with cancerous cells by generating active free radicals which eventually facilitate impairment and rupturing the DNA double-strand which ultimate results in mortality. Further, radiosensitizing agents and radioprotectors are the better alternative options to beat tumor, however, due to their own limitations, novel methodologies has more scope. It is, therefore, a crucial challenge to unravel and to procure a deep understanding of the critical mechanisms of inflammatory caspase-1 and its radioprotecting ability in front of researchers; it may open new doors in the field of radiotherapy to engender novel therapeutic strategies for ameliorating human health in the forthcoming future to the cancerous patient.

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Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

References

1. Ruba T, Tamilselvi R (2018) Radiosensitizers and Radioprotectors for Effective Radiation Therapy. A Review. Asian J Appl Sci 2(1): 77-86.
2. Mohammed JH, Dowlath Sathish KK, Pamela S, Nihala SD, Kantha DA, et al. (2021) Effects of radiation and role of plants in radioprotection: A critical review Sci Total Environ 779: 146431.
3. Prasad MS, Tesla Y, Mahesh BH, Arkaprava R, Yunsu K, et al. (2021) A water-soluble boronate masked benzoindocyanin fluorescent probe for the detection of endogenous mitochondrial peroxynitrite in live cells and zebrafish as inflammation models. Dyes Pigm 191: 10937.
4. Vinutha K, Pavan G (2018) Natural radioprotectors and their impact on cancer drug discovery. Radiat. Oncol J 36(4): 265-275.
5. Deborah EC, James BM (2014) Altering the Response to Radiation: Sensitizers and Protectors. Semin Oncol 41(6): 848-859.
6. Jayam R, Vijay KB, Venkata SK, Uday SR, Venkata S (2014) Radiosensitizers, radioprotectors, and radiation mitigators. Indian J Dent Res 25(1): 83-90.
7. Rahul C, Debojyoti P, Raghavendra SP, Bhakti B, Deepak S, Santosh K (2019) Free Radi Bio Med 143: 560-572.
8. Johnson RJ, Nakagawa T, Sanchez Lozada LG, Yuri Y Sautin, Miguel A Lanaspa, et al. (2013) Sugar, uric acid, and the etiology of diabetes and obesity. Diabetes 62: 3307-3315.
9. Black RA, Kronheim SR, Merriam JE, March CJ, Hopp TP (1989) A pre-aspartate-specific protease from human leukocytes that cleaves pro-interleukin-1β. J Biol Chem 264(10): 5323-5326.
10. Thornberry NA, Bull HG, Calaycay JR, JR Weidner, J Aunins, et al. (1992) A novel heterodimeric cysteine protease is required for interleukin-1β processing in monocytes. Nature 356: 768-774.
11. Martinon F, Tschopp J (2007) Inflammatory caspases and inflammasomes: master switches of inflammation. Cell Death Differ 14(1): 10-22.
12. Veit MS, Akinori O, Shizu I, Madeline RL, Lorenz WJ, et al. (2015) Radiation exposure induces inflammasome pathway activation in immune cells1. J Immunol 194(3): 1178-1189.
13. Gabriel S, Gerhard ES, Martha G, Jennifer S, Hans Dietmar B (2014) Caspase-1: The inflammasome and beyond. Innate Immun 20(2): 115-125.

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