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Editorial

Radiation induced molecular signalling in the cells: A real struggle between death or breathe

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Abstract

Radiation is omnipresent in our surrounding and continuously interacts with us. However, overexposure of ionizing radiation during medical procedures and nuclear accidents has serious concern all over the world. Radiation interacts with biological tissues and deposit its energy resulting in massive oxidative stress leading to cell death. As a result of radiation induced oxidative stress, several pro-survival cell signaling pathways gets activated that provide survival advantages to cancer cells. The predominant signaling pathways that activated upon irradiation include inflammation, cell cycle checkpoints arrest, DNA repair, and apoptosis inhibition. These major signaling pathways are induced through other connected pathways such as PI3K, AKT, ERK Kinase/ERK, Ras, RAF, MEK, phospholipase C/protein kinase C, NfKB, HIF1α, and Jak/STAT pathways and thus decide the fate of the cells. Comparatively, normal cells did not show radioresistance probably due to their controlled proliferation, regulated transcription, and normal metabolism. Hyper activation of cancer cells makes them prone to induce pro-survival signaling resulted radioresistance. Therefore, by identification and validation and evaluation of pro-survival pathways inhibiting drugs in appropriate experimental model may provide a logical solution for more efficient radiotherapy outcome. Whereas, development of pro-survival pathway activators may provide radioprotection to the surrounding normal cells and tissues.

Keywords: Apoptosis, Cell signaling, Oxidative stress, DNA damage, Inflammation

Editorial

Radiation is omnipresent in the universe. Since the primitive period, chemical evolution led to a biological evolution somehow driven by the ionizing and non-ionizing radiation on the Earth's atmosphere [1,2]. Even in the modern era, the cosmic radiation generated is constantly observed in the Earth's outer atmosphere. Accidental or deliberate over imprecise exposure of gamma radiation may lead to serious outcome including death. Past evidences of civilian (Chernobyl and Fukushima nuclear reactor accidents) and several military installations radiation accidents, as well as over radiation exposure during medical procedures [5] and atomic explosion at Nagasaki and Hiroshima are prominent examples, where several hundreds of peoples were affected seriously due to radiation exposure.

At molecular level, high energy gamma radiation interacts with biological macro-molecules i.e., enzymatic and structural proteins, membrane lipids, DNA, RNA, and several molecular complexes and generate free radicals by water radiolysis and thus induce oxidative stress in cellular system. Radiation perturbs functioning of DNA repair proteins, cell cycle regulatory proteins, membrane transport regulating proteins, and most importantly genes transcription and subsequent protein processing regulatory complexes that are mandatory to sustain livingness in the cellular milieu [6]. Although, cells of muscular and nervous systems are relatively expressed resistance against gamma radiation induced mortality, cells of the hematopoietic and gastrointestinal systems are shown higher degree of radio-sensitivity. Even remarkable difference in biological radiation response was reported between non-malignant and malignant cells, normal and transformed stem cells, and proliferating

and non-proliferating terminal cells of similar origins [7,8]. The differential response among cellular systems against ionizing radiation may be decided by the diverse molecular signaling induced by radiation exposure in different cell systems. In general, ionizing radiation exposure lead to following molecular events in sequences i.e., interaction with bio-molecules and cellular water, free radicals generation, oxidative stress induction, membrane and DNA damage, cell cycle arrest, inflammation and immune system modulation, and multiple associated molecular signaling induction, resulted in either cell repairing the damage and survive or if not repaired, cells simply adopt either apoptosis, necrosis, pyroptosis or autophagy mode of death [6].

Signaling Pathways that Provide Safe Escape to the Cells from Death Followed by Ionizing Radiation Exposure

Cell cycle checkpoints response against IR exposure

Radiation induced DNA damage leads to cell death. Radiation may disrupt DNA helix *via* inducing single strand/double strand breaks, sugar and nitrogenous base oxidation, and DNA-protein cross link disruption. As quickly as cells sense DNA damage, it immediately activates cell cycle checkpoints arrest to provide a transient halt in cell cycle progression to repair the genetic damage efficiently. Based on single strand or double strand DNA damage ATM or ATR kinase signaling pathways get activated. These ATM/ATR signaling sensors further activates their downstream components/complexes i.e P53, ChK1/Chk2 kinases, DNA-Pks, CDC25, and P21 etc. Simultaneously, as the results of P^{21} activation, inhibition of Cdk4-Cyclin D, Cdk6-Cyclin D, and Cdk1-Cyclin A and B complexes get activated and resulted in cell cycle checkpoint arrests [9,10]. Cell cycle arrest may provide the supportive environment to the cellular machinery to either repair the cellular damage or if not possible, then cells may adopt death pathways using either, apoptosis, necrosis, pyroptosis, autophagy or senescence mode of cell death [22].

Radiation induced DNA repair signaling activation

Followed by radiation mediated DNA damage, compared to normal cells, cancer cells are known to adopt DNA repair process rapidly to ensure their pace of proliferation. As soon as sensors i.e., ATM, ATR, and DNA-PK sense the DNA damage, they transduce molecular signals to DNA repair complexes to coordinate with repair machinery [7,9]. Irradiated cells immediately activate double strand break (DSB) repair by means of either non-homologous end joining (NHEJ) or homologous repair pathways. NHEJ process of repair first recruit Ku 70/80 proteins at the end of damage DNA strand, then ensure DNA-PKcs joining with the complex and then DNA ligase join the repair complex and initiate DNA repairing [6,11,12]. Apart from DSBs, irradiation also induced single strand breaks (SSBs) in DNA *via* ROS induced oxidation reaction, i.e., oxidative DNA damage [13]. Repairing mechanism of single strand breaks involved multiple signaling pathways including DNA glycosylase based base incision mechanism, and apurine endonuclease 1 (APE1) controlled base incision mechanism [6,14,15]. The post incision base gap is filled by DNA polymerases and the DNA ligase mediated mechanism [16]. Despite very efficient DNA damage repair mechanism is in place, however, the chances of miss-repair are still high that lead to lethal mutation and thus cells end up either with sustained mutation with malfunction and latter transformed in to cancerous cells or not sustain the mutation and adopt the cell death path.

Surviving response of the cells against ionizing radiation exposure

Cells exposed with ionizing radiation are known to stimulate epidermal growth factor receptor (EGFR) tryrosine kinases that further transduce downstream signals *via* its phosphorylation. Downstream signal pathways include PI3K, AKT, ERK Kinase/ERK, Ras, RAF, MEK, phospholipase C/protein kinase C, and Jak/STAT pathways [6,17,18]. Although, all the above-mentioned pathways play significant role in promoting cell survival in irradiated cells, however, PI3K/AKT and Ras-RAF-MEK-ERK signaling have special contribution to avoid radiation induced cell death. Despite a complex cell signaling processes, it can be concluded that Ras-RAF-MEK-ERK signaling collectively provides survival advantage particularly by promoting DNA repair and inhibition of apoptosis induction in irradiated cells. Likewise, PI3K /AKT signaling pathways provide survival benefits to the cells specially by blocking cell death via down-regulating various pro-apoptotic proteins expression at one hand, and up-regulation of the anti-apoptotic proteins expression at another hand [18-20]. NF-κB pathway is also an important signaling pathway, that participates in cell survival after irradiation. NF-κB a transcription factor can activate PI3K/AKT signaling. NF-κB plays significant role in the regulation of inflammatory response against diverse insults including ionizing radiation [17,21]. IκB phosphorylation promotes NF-κB dissociation from it, and translocates towards nucleus of the cell and induced gene transcription that promote cell survival and inhibit apoptosis. The most important transcriptional targets of NF-κB are pro-survival protein i.e., Bcl-2, Bcl-xL, and Mcl-1 expression. Apart from that, NF-κB also modulates gene expression of cell cycle regulating genes like cyclin-D1 that involve in induction of radioresistance in the cancer cells [17].

In general, tumor microenvironment is more hypoxic in nature as compared to surrounding normal tissues [22,24]. Radioprotective activity of hypoxia inducing factor-1α (HIF-1α) has been reported. Hypoxic environment actually did not support HIF-1α degradation, resulted in its activation and initiation of transcription of several target genes that support angiogenesis, autophagy, anti-apoptosis, cancer cells stem-ness properties, and energy metabolism etc., that all signaling processes support radioresistance in cancerous cells [22,23]. Normoxic conditions promote hydroxylation of HIF1α at pro-402 and pro-564 residues that make it prone to interact with von Hippel-Lindau (VHL) E3 ubiquitin ligase resulted in its proteosomal degradation and high radiosensitivity in normal cells [6,25]. Another approach identified that may promote survival benefits to tumor upon irradiation is Yes-associated protein (YAP) signaling. YAP, a transcriptional co-activator for Transcriptional Enhanced Associated Domain (TEAD) family of transcriptional factors is identified to promote radioresistance in the cells [6,27]. YAP phosphorylation at multiple sites provide an opportunity for its binding with 14-3-3 protein and thus ensure its retention in the cytoplasm and proteosomal degradation by ubiquitin ligase complex. However, if YAP retention and degradation in the cytoplasm was compromised, then it translocates into nucleus and interact with TEAD transcriptional factor and activates transcription of several pro-survival, proliferation, energy metabolism, and cancer cells stemness genes [6]. Although, exact mechanism of YAP mediated radioresistance has not been elucidated so far, however, its involvement in the gene expression associated with cell survival i.e., survivine, Bcl-2, Bcl-xL, DNA repair, proliferation, etc. has been

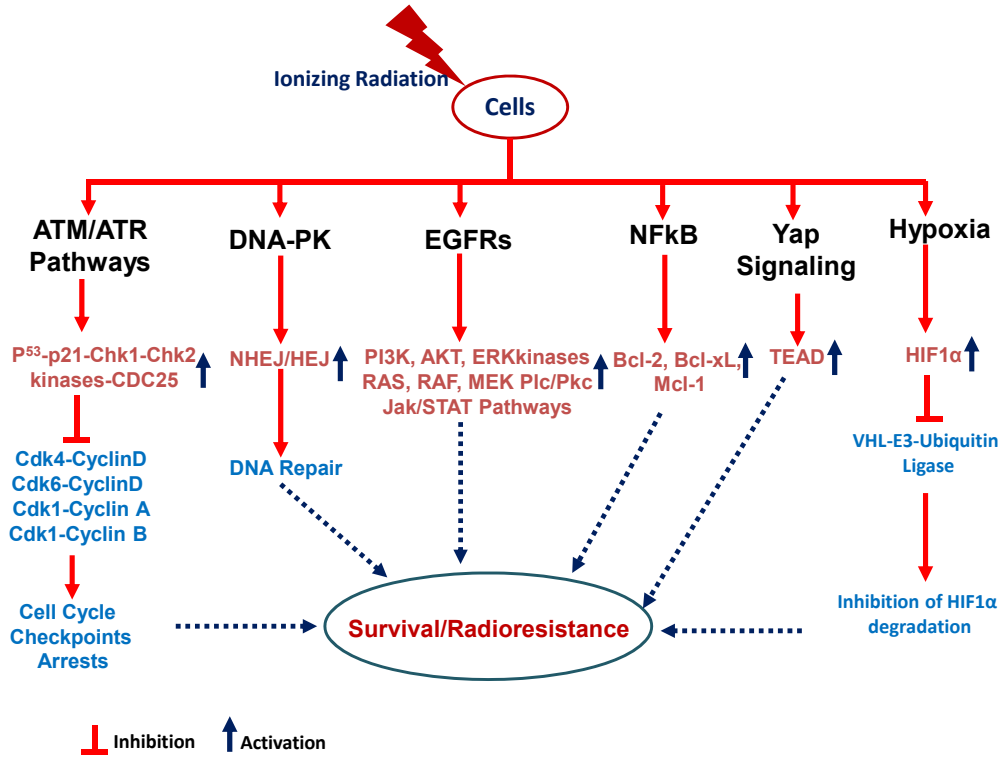

Figure 1. Radiation induced pro-survival/radioresistance signaling pathways in cancerous cells.

reported that created more interest among researcher to understand YAP signaling pathways in more detail. Apart from DNA repair and other survival signaling pathways, gamma radiation also activates the NOD-like receptor proteins i.e., NLRP1 and NLRP3 complex. These complexes subsequently activate caspase-1, pro-inflammatory cytokines i.e., interleukin-1β and interleukin-18, chemokines, tumor necrosis factor-alpha (TNF-α), and high-mobility group protein-1 (HMGB-1). All these events favor the induction of inflammasome signaling and support survival in irradiated cells [28].

In conclusion, ionizing irradiation induce diverse cell signaling in the cancer and normal cells. Several molecular components of the signaling pathways that express differentially in cancerous and normal cells play a very critical role in the decision making by the irradiated cells i.e., either adopt to death or breathe. Though, ionizing radiation treatment promote death of the cancer cells, at the same time, irradiation itself may induced pro-survival signaling such as ATM/ATR/DNA-Pk, DNA repair, cell cycle arrest, PI3K, NFkB HIF-1α and YAP and inflammation associated signaling and thus may activate radioresistance (**Figure 1**). Therefore, fate of the cancerous or surrounding normal cells depends on the activation of signaling pathways upon irradiation. If pro-survival pathway(s) remain dormant upon irradiation, the cell will definitely be forced to adopt the path of death, however, unfortunately, if any of the above identified molecular pathways activated then cell death cannot be ensured and, in this situation, cell may fight to remain alive and breathe. Therefore, to ensure inhibition of pro-survival pathways and best outcome of radiotherapy, specific drug/ inhibitors of the pro-survival pathways must be identified and their efficacy must also be explored as additional adjuvant for radiotherapy of cancer patients.

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