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Radiation Resistance in Radiotherapy : A Review

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Abstract

Radiation resistance is a dual nature phenomena which having both beneficial and harmful effects. If we say in beneficial manner, it develops immunity against radiation which overcomes the risk of cancer. Contrariwise it causes problem during radiation therapy because it made up body resist for radiation. Radiation resistance may occur in naturally (natural climate) and some time it happen synthetically for a purpose. There are several factors which is responsible for radioresistance, here we are discuss all those important factor and their possible mechanism which amenable for it. Factors like NF-KB, over expression STAT 3, TP53 mutation, PI3K pathway activation, AKT/GSK3b/CYCLIN D1/CDK4 Survival Signaling Pathway, cancer stem cells etc are responsible for radioresistance. It is gene based concepts which have a significant role for the treatment of cancer.

Keywords: Radiation resistance, Cancer, DNA damage

1 Radiation Therapy

Radiation therapy usually known as irradiation or radiotherapy is the effective application of various kinds of radiations in order to treat cancer and other diseases. Cancer growth and development and symptomatic relief is achieved by utilizing radiations in therapy by oncologists. This therapy shows its effect via DNA damage in the tumor cells hence, destroying the ability of the tumor to reproduce. These dead cells are naturally excreted by the body. Normal body cells also get degraded due to radiations but, they have the ability to repair themselves in contrast to cancerous cells. Sometimes radiotherapy may be the only option left with the patient or it may just be a part along with other therapies.

2 Types of radiation therapy

- External-beam radiation therapy.
- Internal radiation therapy.

3 Radiation used in radiation therapy

In cancer treatment ionizing radiations are utilized as they form ions in the cells through which they pass. Ions are formed by eradicating electrons from atoms/molecules. This leads to cell damage or genetic change which declines growth of the tumor cells. Radiowaves, visible light waves and microwaves have non ionizing nature. Due to lack of threshold energy these waves cannot produce ions.
There are two kinds of ionizing radiations:

- Photon radiation(gamma rays and x rays)
- Particle radiation(protons, electrons, neutrons, alpha and beta particles)

The penetration into the tissues depends upon the energy possessed by the ionizing radiations which varies with the type of radiation. The property of the waves is an important factor which has to be taken into account while planning treatments. It is the duty of a radiation oncologist to decide the type of radiation best suited for the patient depending upon the cancer type and location.

3.1 Photon radiation

Till date photon beam is the most common type of radiation used in cancer treatment due to its high energy. The sources of photon beam are radioactive in nature such as cesium, cobalt, or a machine known as linear accelerator. These radiations affect the cells through which they pass and then exit from the body. Hence, they must be targeted properly and

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particularly to the tumor cells. These radiations are also used in x-ray machines.

3.2 Particle Radiation

Particle beams or electronic beams are also generated via linear accelerator. Electrons have low energy due to their negative charge. Hence, they cannot penetrate deeply into the body so, these kind of beams are used to treat superficial cancers such as skin tumors.
Proton beams are another form of particle radiation. The positively charged protons release their energy after travelling a particular distance and cause very less damage to the cells through which they pass. Their major action is towards the end of their exit from the body. They hardly damage the nearby cells. This therapy is usually used in routine for particular cancers. The instrument this technique is possible is not widely available. The patient may be exposed to neutrons while applying some of the proton beam therapy techniques.
Neutron beams are used in treating the tumors of the head, prostate, neck and for various inoperable tumors. Neutron has no charge but it may sometimes be used when other form of radiations fail. The targeting of neutron beams is a challenge hence, the use has declined. As the DNA damaged caused by the neutrons is high, the effect on normal cells is also severe.
Carbon ion radiotherapy is useful in treating tumors that become irresponsive to other radiations (radioresistant). It utilizes heavier particle than protons or neutrons hence, it is also known as heavy ion radiation. The particle is the share of carbon atom comprising own protons, electrons and neutrons. Due to its heavy nature it causes more damage to the cells than other radiations. Carbon ion beams may be adjusted like protons to cause the maximum damage to the tumor towards the exit. But, the effects to the normal cells around the tumor are severe. Very few centers in the world offer this facility.
Alpha and beta particles are generated by special radioactive substances which may be swallowed, injected or inserted into the body. Mostly they are used in imaging but are also utilized in cancer treatment.

4 Radiation Resistance in Radiation Therapy

Radio resistance is the property of an organism to resist very high level of radiations. These types of conditions are usually observed with the people working in highly ionized areas due to radiations. Various causes (biological and technical) are related to radio resistance that have been reviewed.

5 Evidence for Radiation Resistance:

5.1 In natural climate

The research of the animals, climate, environment and plants around the very famous Chernobyl disaster area has discovered an unanticipated survival of several species, in spite of high radiation levels. Many radio resistant plants, worms and insects have been found through a Brazilian study in the hilly area of Minas Gerais having high level of radiation due to uranium deposits. Certain extremophiles like tardigrades and bacteria *Deinococcus radiodurans*can resist high dose of ionizing radiations, which may be about 5,000 Gy.

5.2 Induced models

As the minor dose of radiations gets exposed to a person, radio resistant may take place. This has been documented in various studies comprising bacteria, algae, protozoa, yeast, insects, and plants in vitro human and mammalian cells and also in animal models. Various cellular radio protective actions may be involved which involve modifications in levels of certain nuclear and cytoplasmic proteins leading to increase in gene expression, repair of DNA and other progressions.

6 Factors Responsible for Radioresistance

6.1 Transcription Factor NF-κB

Tumor cells have been related to activation of NF-κB which is a transcription factor that increases tumor growth, degrades ionizing radiations as well as resist the chemotherapeutic effect during therapy. Evidences from the past few years also prove that NF-κB is activated *in vivo* and *in vitro* by therapies involving radiations and chemicals. As the NF-κB activates, several genetic changes occurs leading to chemo/radio resistance .The sensitivity of tumor cells towards apoptosis due to chemicals and radiation is directly proportional to NF-κB.

Both the phototonic radiations, Gamma and short wavelength U.V. radiations activate NF-κB by several mechanisms. Gamma rays act by degrading

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IkBa via phosphorylation reaction at sites Ser-32 and Ser-36 while U.V rays based IkBa degradation is phosphorylation independent. Therefore, it is concluded that both of these radiations activate NF-κB via different mechanisms. NF-κB activation has been induced in various cells by chemotherapeutics like vincristine, vinblastine, 5-flurouracil, daunomycin, doxorubicin, paclitaxel, cisplatin, bortezomib and tamoxifen.

After activation, NF-κB binds to κB elements in target genes and regulates the transcription of more than 400 genes which are involved in growth regulation, carcinogenesis, apoptosis, immunoregulation and inflammation. Target genes such as cyclin D1, COX-2, XIAP and surviving which consist of binding sites in region of their promoters regulate the process of radio/chemoresistance in several types of cancer cells. Furthermore, the complete transcriptional triggering of NF-κB may comprise the interaction with other signaling pathways such as protein kinase A, AKT/P13K.

6.2 Overexpression of STAT3

Originally Signal transducer and activator of transcription (STAT) proteins were believed to belong to the family of underlying cytoplasmic transcription factors (CTF) which comprise 7 proteins(STATs 1, 2, 3, 4, 5a, 5b,and 6) responsible for regular cellular responses to growth factors, cytokines and polypeptide ligands. STAT3 regular activation promotes proliferation, tumor growth, tumor cell survival, angiogenesis, invasion, migration and apoptosis inhibition. STAT3 overexpression has been observed in various cancers such as non small cell lung carcinoma (NSCLC). It has also been up-regulated in case of renal cell carcinoma, breast cancer, urothelial cancer, bladder cancer, lung cancer and prostate cancer. Due to its phosphorylation at tyrosine 705, dimer formation, nuclear translocation, binding of DNA and transcription of genes of STAT3 takes place. While, phosphorylation at serine 727 regulates its performance positively or negatively. STAT3 controls the gene expression that affect survival (mcl-1, cellular FLICE- kind of inhibitory protein, bcl-1,survivin), proliferation(c-myc, c-fos, cyclinD1), invading (matrix-metalloproteinase-2(MM2)), and angiogenesis (vascular endothelial growth factor(VEGF)). Radio resistance and chemo resistance have been related to STAT3 activation.

6.3 TP53 mutation and PI3K pathway activation

Evidences show that mutation of TP53 and activation of P13K pathway boosts radio resistance in endometrial cancers where as genes targeting HIF-1α or PI3K/mTOR pathways may improve radiation sensitivity.

6.4 CD133+ cells

CD133 recognizes a cell population based upon certain types of tumors comprising altered DNA repair genetic expression. This expression gets induced on exposure to chemotherapy. The altered genetic expression leads to improved DSB resolution with boost in radioresistance of the cells. Certain DNA repair genes have been recognized which may act as potential therapeutic targets to provide radiosensitivity to cancer stem cells (CSCs).

6.5 B16 melanoma cells

B-1 cells are principally found in the pleural and peritoneal cavities having distinct activation patterns and phenotypic properties which are different for B-2 cells. The role of B-1 and B-2 in tumor progression is still not defined. Some of the studies suggested that direct interaction of B16 melanoma cells and B-1 cells leads to enhanced metastasis in tumors.

6.6 EB virus-encoded latent membrane protein 1(LMP1)

EBV-encoded LMP1 is linked with tumor reoccurrence and poor forecast of nasopharyngeal cancer (NPC). LMP1 enhanced the expression of CD44, which is a CSC marker CD44. But, it is unclear whether the growth of CSCs is induced by LMP1 and the mode of action through which LMP1 enhances radioresistance in NPC.

6.7 Protein FHL2

LIM domains protein 2 (FHL2) is amongst one of the adapter proteins that functions via protein-protein connections and leads to expression that are tumor specific. In 3D grown cell lines and PDAC specimen , FHL2 expression was studied. The contribution of FHL2 in cell cycling, radioresistance and cell survival through its mechanism of action was also studied.

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6.8Hypoxia-inducible factor-2 (HIF - 2)

The impact of hypoxia in solid tumors is declination in chemo/radiotherapy, which is very common. Factors inducing hypoxia (HIF-1,2,3) principally control the response to hypoxia at cellular and organism levels. HIF-2 is amongst the known and established α sub units of hypoxia inducible transcription factors. From previous studies it was clear that HIF-1 was related to chemotherapy failure. But further evidence showed that HIF-2 is also associated with chemoresistance and radioresistance in tumors.

6.9 Loss of RAF kinase inhibitory protein

Damage to RKIP, as observed in initiating PCa tumors and metastasis, provides defense against apoptosis that are radiation-induced. Hence, it is likely to believe that RKIP loss provides an advantage in growth of PCa cells at farther sites, as the degradation of RKIP decreases apoptosis, leading to proliferation.

6.10 AKT/GSK3b/CYCLIN D1/CDK4 Survival Signaling Pathway

One of the important targets of the AKT signaling pathway which is accountable for radioresistance in tumors is Cdk4/cyclinD1. Targeting Cdk4/cyclin D1/GSK3b/AKT pathway would offer an innovative approach to enhance fractionated RT and help in tumor eradication in conjugation with chemotherapy.

6.11 MiR-20a

In case of hepatocellular carcinoma Mia-20a increases cell radio resistance by triggering the AKT/PTEN/P13K signals. Prior studies have revealed that miRNAs are linked with radiosenstivity of tumor, comprising DNA repair proteins, unusual stimulation of multiple signaling routes, and autophagy. Altogether they are involved in various processes which develop radioresistance.

6.12 MiR-95

MiRNAs which act as oncogenes control the expression of various targeted genes after transcription and are involved in pathogenesis and hence, in prediction of cancers. MiR-95 triggers proliferation and radio/chemoresistance via direct targeting sorting nexin1 in non-small cell lung cancer.

6.13 ATF-2

Epithelial cell adhesion molecule (EpCAM) is linked with metastasis in prostate cancer and radio/chemoresistancethrough AKT/TOR/P13K pathway. MET and AKT signaling regulate anti-apoptotic radio resistance in cancer cell lines of head neck.

6.14 Cancer stem cells

Current discovery of cancer cell flexibility and heterogeneity marks CSCs to be a mobile target which would be difficult to track and eliminate. The advent of CSCs in few years for chemo resistance and tumor maintenance has provided novel approaches and vision to study cancer. CSCs have been associated with several human malignancies such as tumors of the lung, brain, pancreas and others. CSCs can be identified using markers that act on cell surface and have the ability to reproduce tumors from small amount of cells. They are phenotypically different from the whole tumor. They are accountable for inducing chemo resistance and metastatic potential in various human cancers and hence, may be responsible for tumor reoccurrence and treatment failure.

6.15 Gliomas

Gliomas are extremely radio resistant with very high relapse capacity. CSCs lead to radio resistance in glioma cells via preferential activating the DNA damage spot check response and an increment in DNA repair potential. The part of cancer cells expressing prominin-1(CD133), a marker for brain CSCs and neural stem cells is augmented after radiation in glioma cells. The Notch mechanism is concerned in deciding the fate of stem cell and cancer. Studies have shown that if Notch pathway is inhibited with gamma secretase inhibitors (GSIs), glioma stem cells become highly sensitive to radiation even at clinically significant dose.

Conclusion

After study of radio therapy it is clear that radiation resistance is a challenging complication of both

radiation and chemotherapy in cancer treatment. There are various genetic changes which may causes radiation resistance weather they are different transcription factor like NF-κB or cancer stem cells, or protein FHL2. All factors are causes radiation resistance by different mechanism with one isonomy that all happen at gene level. In this resistant condition more radiation is required to treat cancer, which may be harmful.

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