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Review Article

Role of oxidative stress in facilitating carcinogenesis

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ABSTRACT

The carcinogenic role of ROS has been a great debate in the past and will be in the future. ROS is produced by both internal (inflammation) and external sources (UV). ROS is important for various important signalling mechanisms for the normal cellular survival. Even though literature exists to support the role of ROS in cancer, the magnitude of its expression and cell type it is expressed will determine whether it plays a positive (apoptosis) or negative role (genomic instability) in cancer. Apart from inducing DNA damage, ROS facilitates carcinogenesis by regulating cell cycle progression, gap junction, inflammation etc. The present review updates the recent discoveries of how ROS regulates these important cellular signalling mechanisms to facilitate carcinogenesis.

Keywords: Bystander effects, Cell cycle, DNA damage, Inflammation, ROS

INTRODUCTION

Cancer is the second leading cause of death and believed to surpass the number of deaths caused by heart diseases in few years.[1,2] Cancer can be caused by mutation in tumor suppressor genes, activation of oncogenes, deregulated signaling pathways and oncoviruses that leads to uncontrolled cell growth and resistance to apoptosis.[3-8] Furthermore, compelling data suggests that tumor cells exhibit increased intrinsic reactive oxygen species (ROS) stress, due to elevated metabolic activity, mitochondrial malfunction and oncogenic stimulation.[9-12]

ROS are generated during normal cellular processes, which balance redox status of cells for their optimal functions. An imbalance between cellular ROS production and their scavengers leads to oxidative stress. This imbalance can be caused through altered regulation of cellular mechanisms, which either generate excessive ROS or affect mechanisms that detoxify these molecules.[13] ROS can be generated through both endogenous (inflammation, mitochondria, metabolism, diet and viral infections) and exogenous sources (ionizing radiation like X rays and ɣ rays, UVA from solar light), and cells balances their harmful effects by several antioxidants like vitamin E, vitamin C, uric acid, glutathione, β-carotene, ubiquinone and detoxifying enzymes like superoxide dismutase (SOD) and etc.[14,15]

Even though oxygen plays an important role in intracellular and extracellular signaling, most of the macromolecules (DNA, lipids, carbohydrates and proteins) of cells are constantly under attack from these ROS molecules, which can lead to damaged cells and tissues. This deleterious effect of ROS culminates activation or dysregulation of several signal transduction pathways that influence on cancer and carcinogenesis. In fact, the early study about role of ROS in cancer was supported by the transformation of normal fibroblast after ROS treatment.[16] Furthermore, influence of ROS is associated with different pathways in cells like cell cycle, senescence, apoptosis, necrosis, angiogenesis, bystander signaling, metastasis and etc. Here we briefly summarize the influence of oxidative stress mediated signals on dysregulation of normal cellular process that leads to cancer.[17-20]

ROS AND CANCER

To first confirm the link between ROS and cancer, we will go through the important discoveries associated with that. Increased ROS expression was documented in various types of tumors.[21] Study carried out in chronic lymphocytic leukemia showed that these patients have an increased expression of ROS.[22] Taking advantage of the discovery, authors tried to increase the cellular oxygen level by inhibiting the antioxidant super oxide dismutase (SOD) or by adding exogenous ROS producing agent arsenic trioxide. Cells isolated from patients with increased ROS showed increased sensitivity to SOD inhibition and arsenic trioxide treatment by showing an increased apoptosis. Similarly, Epstein-Barr virus infected burkitt's lymphoma patient also showed increased expression of ROS.[23] Increased expression of ROS is found in most of cancers including the breast cancer cells.[24]

While the increased expression of ROS is observed in cancer cells, recent studies show an interesting observation that the cancer stem cells have reduced expression of ROS.[25] With less ROS, cancer stem cells can evade the ROS mediated apoptosis, which makes them to survive better than cancer cells.

ROS INDUCED CELL CYCLE PROGRESSION

The eukaryotic cell division occurs through four different phases in cycling cells, namely G1, S, G2 and M. The non-dividing, but viable and metabolically active terminally differentiated cells stay in resting phase in which cells exist in a quiescent state, also known as G0. The actively dividing cells enters the cell cycle, which is tightly controlled by a group of regulatory proteins called cyclins and cyclin-dependent kinases (CDKs) that act at specific phases of the cell cycle and thereby drive the cell from one stage of the cycle to another. Cyclin D in coordination with CDKs 4, 5 and 6 regulates the G0/G1 transition. After entering into the G1 phase, cells start synthesizing necessary mRNAs and proteins for the S phase. Cyclins E and A complexing with CDK 2 regulate G1/S transition. Throughout the S phase a well-controlled DNA synthesis occurs to duplicate the DNA. Cyclin A and CDK 2 regulate the S phase transition. In G2, cells synthesize necessary components required for the M phase. Cyclins A, B and CDK 1 regulate the G2 transition. Finally, in M phase cells divide into two daughter cells.[26] ROS generated through different sources can influence the presence and activity of these enzymes and thereby control the cell cycle progression.[27] Similarly, the effect of ROS-mediated regulation of cell cycle may also depend on their concentration and cell type. The role of oxidative stress in cell cycle progression has been studied in detail. Especially, role of oxidative stress in the vascularization has been documented well. Stably transformed NIH3T3 fibroblasts transfected with ras oncogene showed increased expression of ROS.[28] Both cellular ROS level and mitogenic activity were inhibited by treatment with the antioxidant N-acetyl-L-cysteine. This result confirms that excessive ROS in the cells leads to transformation and abnormal proliferation, which could pave the way for carcinogenesis. Use of antioxidant like ascorbic acid-dehydroascorbate quenched ROS and arrested the cells at G2/M checkpoint.[29] However, not all antioxidants arrest cells at G2/M phase. For example, treatment of cancer cells with antioxidant vitamin C arrests the cells at G1 phase. While inhibition of oxygen stress showed cell cycle arrest, arsenic trioxide mediated induction of oxidative stress showed increased cell cycle progression.[30] Increased expression of oxygen dysregulates spindle assembly, which is important for proper segregation of chromosomes.[31] Dysregulated spindle fibers often result in the aneuploidy and acts as important factor for carcinogenesis. Similarly, continuous expression of H_2O_2 in the ulcerative colitis dysregulates cell cycle checkpoints and activates the cell cycle progression and drives cells into tumorigenesis.[32]

It is interesting to note that ROS can facilitate post translational modification (phosphorylation) of proteins like MAPK, receptor tyrosine kinase and protein kinase B and etc. and facilitate cell cycle progression.[27] Apart from protein phosphorylation, ROS is also found to phosphorylate and activate cell growth receptors like PDGF and EDF, even in the absence of actual ligands receptors.[33] Another important receptor for cell cycle progression that has been activated by ROS is EGFR. Increased expression of ROS inhibits the internalization of EGFR and thus promotes its activity.[34] EGFR over expression is observed in many cancers including ovarian, breast, head and neck and etc. In line with the above observations, inhibition of ROS showed decreased EGFR activity in cancer cells, which confirms role of ROS in cancer cell progression.

While ROS induced cell cycle progression was mostly mediated by targeting signaling molecules, studies also showed that ROS directly acts on proteins that are involved in cell cycle like CDC25. CDC25 is a phosphatase which removes phosphate from cyclin dependent kinase and activates it. It is important for the cell cycle transition from G1 to S phase, as well as G2 to M phase. CDC25 is overexpressed in many cancers and inhibitors of CDC25 are also used to treat the cancers. ROS helps in increased phosphorylation of CDC25 and its function in cell cycle progression.

Apart from protein phosphorylation, ROS also showed to alter ubiquitination process. Especially, increased ROS ends up in inhibition of ubiquitin activating E1 and ubiquitin conjugating E2 enzymes. Protein ubiquitin is important for the proteosomal degradation, thus inhibition of ubiquitin by ROS often results in increased expression of proteins, which include cell cycle proteins and results in the increased cell cycle progression and cancer. Cyclin A is one of the ubiquitin targets for ROS. Increased cyclin A facilitates the cell cycle progression from G1 to S phase. Treating the fibroblast cells with

antioxidants actually prevents the accumulation of cyclin A and inhibits the cell cycle progression.[35]

Regulation of cell cycle is an important mechanism that is essential to maintain normal cellular homeostasis. However, when cell cycle is initiated in an uncontrollable fashion, then it leads to carcinogenesis. ROS regulating cell cycle in a pro-proliferation manner is a big concern. Because, whenever normal cellular homeostasis is affected by either endogenous or exogenous source, it directly or indirectly alters the cellular redox state and induces oxidative stress. Even though using antioxidants is the main counter action available to suppress oxidative stress, detailed study of how ROS regulates the cell cycle and its influence in cancer is yet to be analyzed.

ROS INDUCED CHANGES IN THE GAP JUNCTION

Cellular gap junctions are formed by a hexamer of connexin proteins with a central pore size of 1.5 to 2 nm, which permit passage of molecules up to 10-15 KDa in size. Gap junctions are formed when connexons (composed of six identical connexin protein) on adjacent cells dock to form a pore between cells allowing cytoplasmic continuity. Phosphorylation of connexin was reported to regulate the communication between cells 36. Evidence for the involvement of GJIC in mediating bystander response had been generated using gap junction inhibitors such as: lindane, filipin and octanol; as well as genetic approach with connexin-43 (-/-) mouse embryo fibroblasts.[37]

Normal cells tend to be in contact with cancer cells via gap junction, mainly to transmit the signals to contain their abnormal growth. However, cancer cells can overcome these signals from normal cells by reducing the gap junction interaction between them. Increased ROS in cancer cells showed decreased gap junction interaction.[38] Increased expression of oxygen radicals like H_2O_2 decreases the gap junction formation. Furthermore, treating cells with antioxidant made these cells to re-express the gap junction. Thus, ROS becomes a major signaling factor that is important for cancer cells to overcome the growth inhibiting signals from normal cells. Normal cells irradiated with α particle showed increased cell killing. Authors also observed that inhibition of gap junction or ectopic expression of antioxidant glutathione peroxidase reduced cell killing effect of the radiation. This result confirms that the ROS acts as DNA damage amplifying factor in response to radiation via gap junction signaling.[39] ROS induced inhibition of cell-cell communication also helps the cancer cells to promote angiogenesis by promoting the growth of endothelial cells. In this recent research, conditioned media from breast cancer cells reduced gap junction in vascular smooth muscle cells.[40] Similarly, siRNA knockdown of connexin, a protein important for gap junction also showed similar downregulation of gap junction.[43] Even though the link between ROS and downregulation of gap junction has been not analyzed in this study, it is a obvious link that ROS can down regulate gap junction and downregulation of gap junction leads to endothelial proliferation. This results in functional angiogenesis formation for tumor cells to survive.

It is also important to note that when cancer cells are metastasized, it must disintegrate itself from its cell-cell communication. To disintegrate form the cell-cell communication, cancer cells first must overcome their gap junction communication. Reduced gap junction has been well connected with increased invasion and metastasis of cancer cells. Overall, the findings confirm that increased ROS is associated with reduced gap junction formation, which in turn is associated with increased invasion and metastasis. Invasion and metastasis is one of the important hallmarks of cancer and often results in aggressive form of tumor, which is not easy to treat.

ROS INDUCED CHANGE IN DNA REPAIR

Increased DNA damage and damaged cells inability to repair the damage often results in accumulation of genomic instability and carcinogenesis.[41-43] ROS induced DNA damage and its relevance to cancer is well established. Most of the ROS induced damages to DNA are base damages and are mostly repaired by base excision repair (BER) mechanism. Especially, 8-hydroxydeoxyguanosine (8-oxoG) and formamido-pyrimidines are the most common damages induced by ROS. Defective in the repair of ROS induced base damages by BER often leads to diseases such as premature aging, metabolic disorders and most importantly cancer.[44,45]

ROS induced base modifications are dangerous when it happens in tumor suppressor genes or oncogenes. Tumor cells show increased ROS compared to normal cells.[21] Another important observation the strongly supports the role of ROS in cancer is that decreased expression of antioxidants like catalase and superoxide dismutase compared to normal cells.[46] In another way, ROS can induce mutations in cancer cells that are critical for cancer cells to become metastasized.[47] Immuno-histochemical analysis of normal mammary tissue, benign hyperplasia (BH), ductal carcinoma in situ (DCIS) and invasive breast cancer (IBC) revealed increased expression of oxidative stress proteins like SOD1, Ape1/Ref-1, Trx, and PDI are over expressed in cancer cells compared to the normal cells.[48] While increased expression of these proteins confirms that cancer cells are under constant oxidative stress, increased expression of DNA damage marker ɣH2AX and DNA repair protein Ape1/Ref-1 was also observed in the cancer cells compared to their normal counter parts. It is important to note that the increased expression of DNA repair proteins will also lead to increased DNA repair that might help the cancer cells to acquire chemoresistance.

In lung cancer, cigarette smoking also showed increased formation of 8-oxoG in the lung cancer patients compared to control patients.[49] The increased 8-oxoG must be due to increased oxidative stress in the lungs which are exposed to nitrosamines and polycyclic aromatic hydrocarbons during smoking. Similarly, oral cancer patients with tobacco chewing habit showed increased oxidative stress.[50] Both the smoking and tobacco chewing causes an imbalance in regulation of oxidative stress leading to increased oxidative stress. Especially, increased lipid peroxidation and DNA damage induced by oxidative stress will certainly increase the risk of cancer in these patients.

Increased oxidative stress is found in most of the cancer predisposition diseases like Ataxia-Telangiectasia, Fanconi Anemia, Down syndrome, progeroid syndromes, Beckwith-Wiedemann syndrome, and Costello syndrome. However, recent study suggests that increased oxidative stress in these DNA repair deficient diseases increases the risk of mitochondrial dysregulation. Dysregulation of mitochondria will be one of the early effects of oxidative stress and the persistent dysfunctional mitochondria results in the cancer formation. Authors also suggested that targeting mitochondria in the cells that have pro oxidation state could be a potential therapeutic approach.[51]

Apart from the endogenous ROS induced DNA damage, certain chemicals like arsenic increases the level of ROS and DNA damage. Recent study identifies that the increased exposure of arsenic, especially in the skin, induces mitochondrial DNA damage and results in carcinogenesis.[52]

DNA repair is an important cellular process which is controlled by various signaling factors. The critical role of DNA repair for healthy environment is that it should be active in normal cells and inactive in the cancer cells. Active DNA repair in normal cells will allow the cells to repair the damages and stay healthy, while active DNA repair in cancer cells will often result in repairing of chemotherapeutics induced DNA damage and induce chemoresistance.[53,54] Thus makes all the regulators of DNA repair mechanism including ROS, an important messenger for normal cell survival. Since the cells response to ROS varies based on cell type and magnitude of ROS formation, complete analysis of ROS in cells with different genetic background has to be analyzed in detail. Moreover, activation of apoptosis by ROS and its mechanism should also be decoded in detail to draw a link between repair and survival of the cancer cells.

ROS INDUCED CHANGE IN INFLAMMATION

ROS production is one of the early responses of host innate immunity against microbial invaders.[55] Several microbes that are pathogenic to human and animals and their toxins that activates host immune system have shown their efficacy against cancer.[56–60] Alteration of ROS levels with the help of microbes suggested as a conserved strategy to tackle several diseases. Further, regulation of cellular ROS by microbes can be crucial in chronic inflammatory diseases such as cancer.[61,62] Continuous exposure to ROS species often results in chronic inflammation and results in life threatening diseases including cancer. Increases oxidative stress leads to activation of various transcription factors like AP-1, HIF-1α, NF- κB, p53, β-catenin/Wnt, PPAR-γ, and Nrf2. Activation of these transcription factors in turn activates inflammatory cytokines and chemokines, which have the potential to transform the normal cells into tumor.[63] Strong epidemiological and experimental data supports the fact that inflammation and cancer is closely related.[64]

Recent study conducted in breast cancer tissues shows increased expression of inflammatory cytokines like COX-2, IL-1β, IL-8, and TNF-α compared to the normal tissues.[65] Moreover, the study showed increased expression of ROS and DNA damage in cancer tissues. Another study showed increased breast cancer incidence in patients who have taken oral contraceptives.[66] Interestingly, these patients who were taking oral contraceptives showed increased ROS, as well as increased expression of C-reactive protein, a marker of chronic inflammation. Another important organ that is under constant attack from inflammatory cytokines is gastrointestinal tract. Since it has to support the potential source of ROS like intestinal flora, immune cells and dietary products, this organ is more prone to ROS attack. Similarly, increased expression of ROS is observed in chronic inflammatory bowel disease such as ulcerative colitis or Crohn's disease. These patients have 6-fold increase in the risk of colorectal cancer compared to the control patients.[67] These results confirm the link between inflammation, ROS, DNA damage and carcinogenesis.

Inflammation in esophagus (Barrett's esophagus) increases the risk for esophageal adenocarcinoma. Recent study showed increased expression of C-reactive protein, IL6, TNF receptors I and II and also oxidative stress marker F2-isoprostanes in patients with Barrett's esophagus. While the increased expression of C-reactive protein and IL6 showed significant increased risk to esophageal cancer, TNF receptors and F2-isoprostanes did not show any significant increase in the risk to esophageal cancer. This result urges the researchers to further confirm the role of ROS and its influence in inducing inflammation or inflammation induced ROS in inducing esophageal cancer.[68]

Another important hallmark of cancer is angiogenesis, which is the formation of new blood vessels to supply nutrients to solid tumors. It is interesting to note that angiogenesis is regulated by increased ROS and chronic inflammation.[69] For example, during inflammation the arachnoid acid is converted into prostaglandins, which in turn activates various inflammatory cytokines. These inflammatory cytokines increase the production of ROS and assists in proliferation of endothelial cells or

angiogenesis. Overall results confirm that increased oxidative stress will lead to inflammation and increased inflammation also leads to increased ROS, however both ROS and inflammation have a major role in carcinogenesis independently as well as co-independently.

Finding the appropriate antioxidant that also serves as anti-inflammation will be a better approach to treat cells for chemoprevention. Though various molecules that serve as both antioxidant and anti-inflammation are currently being used for various conditions like rheumatoid arthritis or diabetes, effects of these molecules in patients with inflammatory disorder has to be evaluated in detail to avoid the initiation of carcinogenesis.[70,71]

CONCLUSION

ROS has been shown to induce both beneficial and harmful effects in cells. While the level of ROS and cell types in which it is measured is important to confirm its role, increased expression of ROS mostly results in assisting carcinogenesis. As briefed earlier, increased expression of ROS leads to increased cell cycle proliferation, decreased gap junction, altered DNA repair and increased inflammation. Using of antioxidants is considered the best way to inhibit this ROS. However specific and focused studies have to be performed to not disturb the beneficial activity of ROS but to target only the ROS which is expressed in non-homeostatic manner, which poses a threat to normal cell function. Especially, detailed study of mitochondria, which is the primary source of endogenous ROS production, has to be studied in detail.

Analyzing novel pathways and mechanism to inhibit the mitochondria mediated expression of ROS will give a better idea to understand the role of ROS. Using naturally available antioxidants in patients with various inflammation diseases must be evaluated, so that it can be actively used as chemo preventive agents to avoid the ROS and inflammation induced carcinogenesis. Similarly, how ROS regulates the DNA repair mechanism must also be studied in detail. While active DNA repair is good for normal cell survival, it can induce chemoresitant phenotype in cancer cells. Since most of the DNA repair proteins get activated only after post translational modification, it is important study how ROS is involved in this process. Finally, natural or synthetic novel antioxidants that have strong potential to inhibit increased ROS overexpression must be evaluated in the normal, inflammated and cancer tissues. The results will give a better understanding of how ROS inhibition can make the cells less susceptible to carcinogenesis.

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