

KEY FACTORS ASSOCIATED WITH CANCER PROGRESSION: A REVIEW

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Abstract: Cancer is the continual unregulated proliferation of cells mainly due to changes in fundamental functioning of cell. In place of responding normally to the signals that control normal cell behaviour, cells in cancers condition grow and divide in an uncontrolled manner, invading normal tissues and organs and eventually spreading throughout the body. There are numerous factor involved in development of pathological condition of cancer and conversion of normal cells into cancers cells like reactive oxygen species (ROS), apoptosis, NF-kB, autophagy, immunity, metabolism etc. In this review we have discussed the involvement of various key factor that control the growth of cancers cell and responsible for pathological condition of cancer.

Key words: Cancer, Autophagy, NF-kB, Immunity

INTRODUCTION

Normal cellular functioning is controlled by various cellular factors which all together make complex signalling pathway network within the cell. This complex network regulate cell proliferation whenever it required in body such as wound healing condition, normal cell division in various tissue. But when these signalling pathways get off track by over activation or suppression of any one or more factor tissue lead to develop in cancers condition [1]. Targeting one or more of these factors involved in signalling pathway would be valuable to develop therapy for cancer treatment. In this review we are focusing on various factors involved in regulation of cancer signalling pathway, what are their role in normal cell growth and function and how they involved in tumorigenesis. Table 1 shows the key factors involved in mutagenesis.

Reactive oxygen species (ROS): Reactive oxygen species (ROS) is a natural by-product of the

metabolism of oxygen and have important roles in cell signalling and homeostasis. Initially, increased level of ROS, promote cell proliferation and differentiation, further excessive amount of ROS induces oxidative damage to lipid, protein and DNA. Increased concentration and duration of exposure causes cellular genomic instability and activation of various signalling cascades related to cancer [2].

ROS can promote carcinogenesis by DNA damage, leading to activation of oncogenes or inactivation of tumor suppressor genes. For example, H₂O₂ induces activating mutations in the human c-Ha-ras-1 protooncogene [3] and inactivating mutation of the tumor suppressor p53 gene [4].

ROS also induce tumorigenesis by mediating various epigenetic alterations. Methylation and inactivation of tumor suppressor genes is common epigenetic alterations in oxidative stress-induced tumorigenesis. In many studies H₂O₂ has been shown to down-regulate the expression of E-cadherin (a cell-cell

adhesion molecule) tumour suppressor in hepatocellular carcinoma cells which are mediated via snail mediated hypermethylation of E-cadherin promoter region by recruiting histone deacetylase 1 (HDAC1) and DNA methyltransferase 1 (DNMT1) [5]. Down expression of E-cadherin causes increase metastasis and poor prognosis in hepatocellular carcinoma [6].

ROS also can affect angiogenesis through mediating generation of H₂O₂ by NOX4 mediates EC proliferation, whereas NOX2 prevents apoptosis and promotes EC survival [7]. Similarly, ROS has been involved in vascular endothelial growth factor (VEGF)-mediated phosphorylation of cadherin/catenin cell-cell adhesion complex. Phosphorylation of cadherin/catenin by ROS result in disassembling of EC, hence, is facilitating its cellular migration [8].

ROS control VEGF (Vascular endothelial growth factor) signalling through different ways in order to spreading cancer to other cells: (1) induction of transcription factor HIF-1 α , leading to the up-regulation of VEGF and VEGF receptor expression [9], (2) activation of VEGF receptors, either upstream or downstream, to various angiogenic signalling cascades such as PI3K/Akt and MAPK pathways [10] and (3) inhibition of prolyl hydroxylase, leading to the stabilization of HIF 1 α , which in turn leads to VEGF activation [11].

Apoptosis: Apoptosis is a programmed cell death which has a critical role in the development and homeostasis in normal tissues by various pathways. It helps to elimination of unnecessary and unwanted cells to maintain the healthy balance between cell survival and cell death [12]. Defects in programmed cell death (apoptosis) mechanisms play important roles in tumor pathogenesis which allow cancers cells to survive over intended life spans, subverting the need for exogenous survival factors and providing protection from oxidative stress and hypoxia as the tumor mass grow. All together lead to accumulation of genetic alterations that deregulate cell proliferation, interfere with differentiation, promote angiogenesis, and increase invasiveness during tumor progression. Defects apoptosis also responsible for activation of proto oncogene and many deregulated oncoproteins drive cell division and trigger apoptosis [13].

Normal cell repair their DNA by them self but in cancers condition defects in DNA repair and/or

chromosome occur which normally trigger cell suicide as a defence mechanism for eradicating genetically unstable cells and thus such suicide mechanisms defects permit survival of genetically unstable cells, providing opportunities for selection of progressively aggressive clones and promote cancer. Normally cancers cells acquire resistance to apoptosis by the expression of antiapoptotic proteins such as Bcl-2 or by the down regulation or mutation of pro-apoptotic proteins such as BAX. Since the expression of both Bcl-2 and BAX is regulated by the p53 tumor suppressor gene, some forms of human B-cell lymphoma have Bcl-2 over expression. That example represents the first and strongest lines of evidence that failure of cell death contributes to cancer. Apoptosis defects also promote epithelial cells to survive in a suspended state, without attachment to extracellular matrix which facilitates metastasis [14].

In apoptotic cancer condition some molecule like c-FLIP, cellular FADD-like interleukin-1beta-converting enzyme inhibitory proteins, which regulate caspase-8 activation, act negative regulator of apoptosis in human cancer cells. Despite the identified dual functionality of c-FLIPL as a pro- or anti-apoptotic factor in normal tissues, c-FLIPL has generally been shown to act as a key negative regulator of apoptosis in cancer cells. Apoptotic cancer where over expression of c-FLIP take place are melanoma, hepatocellular carcinoma, small cell lung carcinoma, and endometrial, colon and prostate cancer [15].

NF- κ B: NF- κ B (nuclear factor kappa-light-chain-enhancer of activated B cells) is a protein complex which is important for transcription of DNA, cytokine production and cell survival. NF- κ B is found in almost all animal cell types and is involved in cellular responses to stimuli such as stress, cytokines, free radicals, heavy metals, ultraviolet irradiation, oxidized LDL, and bacterial or viral antigens. NF- κ B also regulate the immune response to infection. Approximately 15 – 20% of human cancers are linked to NF- κ B, the role of dysregulation of NF- κ B has been established to cancer. NF- κ B has also been implicated in processes of synaptic plasticity and memory. NF- κ B is a transcription factor that consists of heterodimers or homodimers formed by the members of the NF- κ B family. NF- κ B is activated by a variety of cancer-promoting agents and with inflammatory cytokines NF- κ B play important for inflammation-associated cancer development [16]. NF- κ B activates several genes that affect cancer

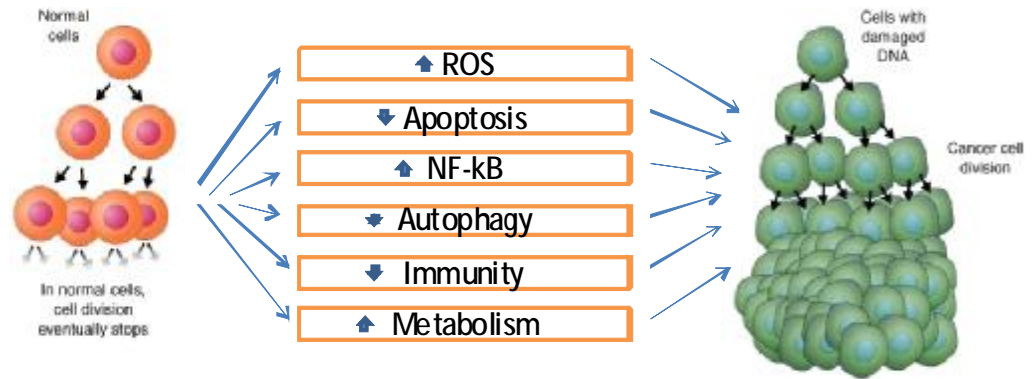


Table 1: Key factors involved in conversion of normal cell into cancers cells

cell migration and invasion and angiogenesis. NF- κ B induces EMT-related genes such as Twist, intercellular adhesion molecule-1 (ICAM-1), endothelial leukocyte adhesion molecule 1 (ELAM-1), vascular cell adhesion molecule 1 (VCAM-1), MMPs, and serine protease urokinasetype plasminogen activator (uPA) and epithelial–mesenchymal transition (EMT) in tumor cell for invasion and metastasis [17]. NF- κ B is considered as a cell survival factor because it confers cell survival. NF- κ B targets cIAP-1 and cIAP-2 function which directly binding and suppressing the effector caspases that are important for recruitment and activation of IKK in cancers cells [18].

Autophagy: Autophagy is a cellular catabolic degradation response to starvation or stress whereby cellular proteins, organelles and cytoplasm are engulfed, digested to maintain cellular metabolism. Autophagy is also a pathway that is used for the elimination of pathogens and for the engulfment of apoptotic cells. Autophagy is responsible for tumour suppression by allelic loss of the essential autophagy gene beclin1 in many type of cancer such as breast, ovarian and prostate cancers [19]. Autophagy also play a role in maintaining tumour cell survival in response to metabolic stress *in vitro*, and in hypoxic tumour regions *in vivo* where cell regulate the mutually opposed survival-supporting and death-promoting roles. Autophagy promotes tumorigenesis by the stimulation of necrotic cell death and an inflammatory response in tumours with defects in autophagy and apoptosis [20].

Preventing survival under starvation through autophagy, and diverting apoptosis-defective tumour cells to a necrotic cell fate, generates chronically necrotic tumours. These disturb normal wound-healing response and support tumour growth, representing a possible means by which autophagy defects provide a non-cell-autonomous mechanism for stimulating tumorigenesis. In cancers inducing process autophagy combined with the immune system and tumour micro-environment to convert normal cell to cancers cell. In contrast to apoptosis, necrosis and cell lysis causes nuclear HMGB1 to be released from cells, and this and other events stimulate the innate immune response, the recruitment of inflammatory cells, cytokine production and nuclear factor- κ B (NF κ B) activation, which increases tumorigenesis [21].

In place of blocking autophagy after activation of Akt in apoptosis-defective cells results in necrosis in response to metabolic stress *in vitro*, and in tumours *in vivo* this necrosis is coincident with NF- κ B activation and promotion of tumorigenesis. Increased rate of cellular damage accumulation causes defective autophagy and compromised survival to stress can promote tumour progression despite reduced cellular fitness. Autophagy control the accumulation of genome damage and suppresses the mutation rate by maintaining energy homeostasis or preventing the damaging effects of oxidative stress from defective organelle and unfolded protein accumulation [22].

Immunity: The immune system protects the body against illness and infection caused by bacteria, viruses, fungi or parasites. Cancer weaken the immune system by spreading into the bone marrow. The cancer cells in their surrounding areas release different immune cells such as contains innate immune cells (including macrophages, neutrophils, mast cells, myeloid derived suppressor cells, dendritic cells, and natural killer cells) and adaptive immune cells (T and B lymphocytes) (which consists of fibroblasts, endothelial cells, pericytes, and mesenchymal cells) [23]. These different immune cells communicate with each other by means of direct contact or cytokine and chemokine production and control tumor growth. The growth of tumor is control by the expression of various immune mediators and modulators as well as the abundance and activation state of different cell types in the cancers organ [24].

The most frequently found immune cells in cancer are tumor-associated macrophages (TAMs) and T cells. TAMs promote tumor growth and important for angiogenesis, invasion, and metastasis, while high TAM content generally correlates with poor prognosis. Mature T cells get divided into two major groups based on the T cell receptors (TCR) they express: $\gamma\delta$ and $\alpha\beta$. $\alpha\beta$ T cells are further classified according to their effector functions as CD8+ cytotoxic T cells (CTLs) and CD4+ helper T (Th) cells, which include Th1, Th2, Th17 and T regulatory (Treg) cells, as well as natural killer T (NKT) cells. Increased T cell numbers specifically activated CTLs and Th cells control survival of cancers such as invasive colon cancer, melanoma, multiple myeloma, and pancreatic cancer [25]. T cell deficiency or disruptions of specific cytotoxic mechanisms make

body more susceptible for spontaneous or chemical carcinogenesis. While many studies suggest that T cell types found in solid tumors are involved in tumour promotion, progression, or metastasis, including CD8+ T cells, IFN γ -producing Th1 cells, Th2 cells and Th17 cells [26].

Metabolism: Metabolism generates oxygen radicals, which contribute to oncogenic mutations. Activated oncogenes and loss of tumor suppressors in turn alter metabolism and induce aerobic glycolysis. Aerobic glycolysis is responsible for high rate of glucose fermentation to cancer. Glutamine with glucose via glycolysis provides the carbon skeletons, NADPH, and ATP which facilitate building of cancer cells, which persist in hypoxia that in turn rewires metabolic pathways for cell growth and survival. High caloric intake is associated with an increased risk for cancers and less caloric is protective by clearance of mitochondria or mitophagy, thereby reducing oxidative stress [27].

There are many studies which indicate normal cell conversion in cancer cell is associated with metabolism. In cancer increasing number of cancer cells with local low nutrient and oxygen levels trigger the growth of new blood vessels into the neoplasm. Like stromal cells cancer cells also recycle and maximize the use of nutrients. The role of hypoxia in cancer cell metabolism in the context of tumorigenesis has been established since it is essential for survival and progression of a tumor, imperfect neovasculature in the tumor bed is poorly formed and inefficient which lead to hypoxic stress [28].

Metabolic conditions such as obesity, hyperglycaemia, hyperlipidaemia and insulin resistance all are associated with an increased risk of developing various types of cancer, accelerated tumour progression. High circulating levels of glucose, insulin and insulin-like growth factor 1 (IGF1) promote tumour growth by stimulating both mitogenic signalling pathways through IGF1 receptor (IGF1R) and glucose uptake by malignant cells. Alter metabolism of cancer cells is associated with the activation of proto-oncogenes and to the inactivation of tumour suppressor genes and accumulation of specific metabolites such as succinate, fumarate and 2-hydroxyglutarate (2HG) also lead to oncogenesis through altering specific signal transduction cascades [29].

CONCLUSION

Here in this article we wish to emphasize key factors whose unregulated behaviour convert normal cells into cancer cells. In view to make better understanding toward the cancer pathology and search for better therapeutic target for cancer treatment. The information related to cancer pathways and their controlling factor can be used to search novel therapeutic strategies, based on the combination of different signalling pathways regulator. The progress in the fight against cancer will depend on how much we understand the critical factors involved in cancer development at the molecular level and linking that to the development of drugs that can interfere selectively with these events.

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