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Review Article

Cancer: A New Era for cancer prevention

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Abstract
We are currently on the brink of a new era in the understanding, detection, diagnosis and treatment of cancer. Drawing on new findings from diverse areas of research – ranging from cell biology, to biophysics, to epigenomics – the current thinking about the origins of cancer is undergoing a revolution, driven by technical and methodological advances. In this review we discuss recent progress made in cancer research work and hypothesis in prevention of cancer. Accumulating evidence has implicated that development of NF-κB targeted gene therapy and the evolution towards clinical application and cyclooxygenase (COX-2) inhibitor i.e. nonsteroidal anti-inflammatory drugs (NSAIDs) prevent colon and possibly other cancers has spurred novel approaches to cancer prevention. DNA Damage Repair and Response Proteins as Targets for Cancer Therapy, Cancer Stem Cells, Role of chelates in treatment of cancer and Mcl-1 plays a critical pro-survival role in the development and maintenance of both normal and malignant tissues, as well as use of peptides in cancer treatments.

Keywords: - COX, Cancer Stem Cells, DNA damage repair mechanism, Mcl-2.

Introduction
The success of an organism to survive from one generation to the next is largely dependent upon the fidelity of replication of its genetic material, deoxyribonucleic acid (DNA). Unfortunately, DNA in living cell is labile and subject to many chemical alterations, and these alterations, if not corrected, can to lead to diseases such as cancer[1].

Cancer Stem Cells (CSC)
Accumulating evidence has implicated that cancer is a disease of stem cells. A small fraction of cancer cells adopt the properties of stem cells. Current evidences have pointed out the cancer stem cells a broad group of cells that share some common properties, such as self-renewal and the ability to maintain a tumour. The self-renewal and multilineage differentiation characteristics of stem cells are due to genetic programme that is common to stem cells of all origins. Maria Perez-Caro and Isidro Sanchez-Garcia has discussed that the gene expression similarities in the common properties between stem cells, in the common properties between stem cells, in the last years we have been led to the development of an *in vivo* genetic cancer stem cell mouse model system, based upon alterations in cancer stem cells able to recapitulate the human cancer pathology. Authors group has shown that CSCs from different cancer types are similar, implying that a similar therapeutic approach could be used in many different cancers. The challenge is now to find a way to specifically target CSC without causing toxicity to normal cells[2].

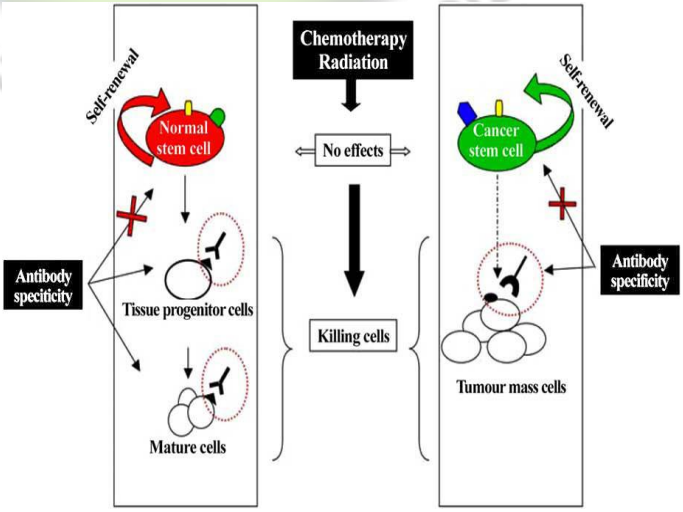

Fig. (1). Current anticancer therapies in the stem cell/cancer stem cell and mature cell populations.

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The increasing idea of the cancer stem cells being the source of origin of cancer has swayed the recent therapeutic intervention directed to the cancer cell mass. If cancer results from cancer stem cells, characterised by very low rates of proliferation and division, it has become clear that therapies such as chemotherapy or radiation, were dependent on high division and proliferation rates, and new antibodies designed against mature cell antigens, would not be effective at targeting CSC.[2]

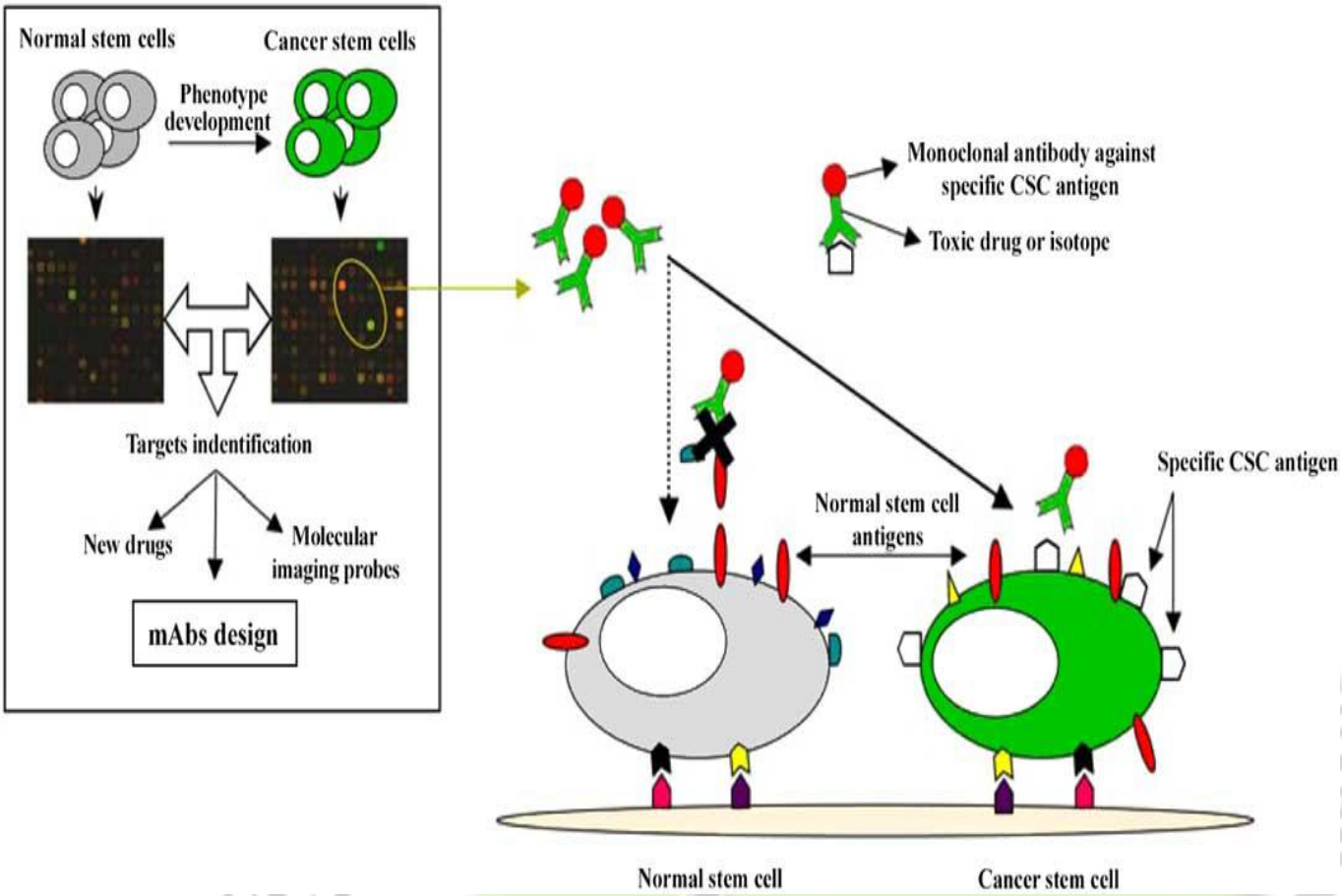

Fig. (2). Using CSC gene expression profile in the generation of therapeutics mAbs. Creation of modified mAbs with more human characteristics in the last years has allowed the efficient binding of these with the receptors expressed on immune effector cells. The identification, using gene expression profiles of new functional targets and epitopes on cancer stem cells from our CSC mouse models, would allow us to generate improved specific inhibitory antibodies capable to recognise and eliminate cancer stem cells responsible for the maintenance of the cancer cell population.[2]

Cancer Prevention: A New Era beyond Cyclooxygenase-2

The seminal epidemiological observation that nonsteroidal anti-inflammatory drugs (NSAIDs) prevent colon and possibly other cancers has spurred novel approaches to cancer prevention. The known inhibitory effect of NSAIDs on the eicosanoid pathway prompted studies focusing on cyclooxygenase (COX) and its products. The increased prostaglandin E2 levels and the over expression of COX-2 in colon and many other cancers provided the rationale for clinical trials with COX-2 inhibitors for cancer prevention or treatment. There is evidence to suggest that COX-2 may not be the only or ideal eicosanoid pathway target for cancer prevention. Six sets of observations support this notion: the relatively late induction of COX-2 during carcinogenesis; the finding that NSAIDs may not require inhibition of COX-2 for their effect; the modest effect of coxibs in cancer prevention; that currently available coxibs have multiple non- COX-2 effects that may account for at least some of their efficacy; the possibility that concurrent inhibition of COX-2 in non-neoplastic cells may be harmful; and the possibility that COX-2 inhibition may modulate alternative eicosanoid pathways in a way that promotes carcinogenesis. Authors suggest that targets other than COX-2 should be pursued as alternative or complementary approaches to cancer prevention.[3]

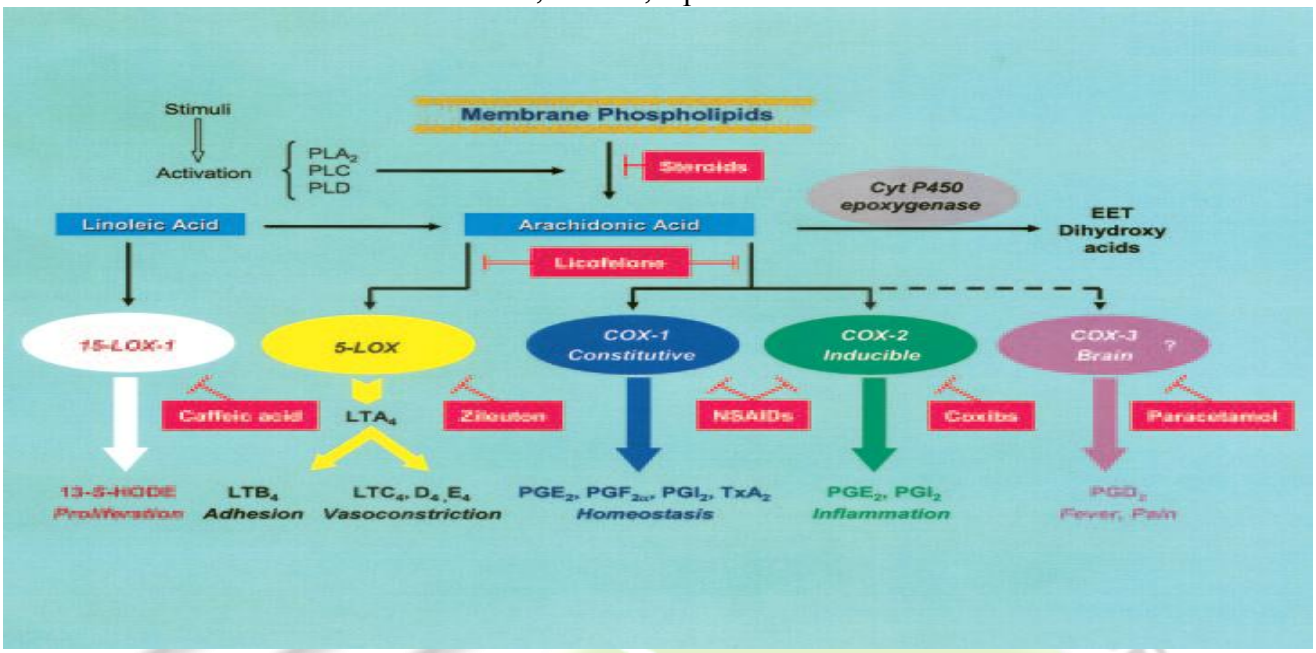

Fig. (3). Overview of the eicosanoid pathway. Arachidonic acid, the substrate of three major biosynthetic pathways, is derived from diet and released from membrane phospholipids through a series of reactions requiring phospholipases, or synthesized from linoleic acid. The COX pathway produces various eicosanoids and thromboxane; the LOX pathways produce leukotrienes and hydroxyeicosatetraenoic acids; and the cytochrome P450 pathways produce epoxyeicosatrienoic acid (EET) and dihydroxyacids. PLA2, PLC, and PLD, phospholipases A2, C, and D, respectively; PGE2, PGF2_, PGD2 and PGI2, prostaglandins E2, F2_, D2, and I2 (prostacyclin), respectively; TxA2, thromboxane A2; LTA4, LTB4, LTC4, LTD4, and LTE4, leukotrienes A4 , B4, C4, D4,and E4, respectively; 13-*S*-HODE, 13-*S*-hyroxyoctadecadienoic acid. T-shaped arrows, inhibition; broken arrow, putative pathway.[3]

Gene Therapy Targeting Nuclear Factor (NF) - κB

Nuclear factor (NF) - κB is regarded as one of the most important transcription factors and plays an essential role in the transcriptional activation of pro-inflammatory cytokines, cell proliferation and survival. NF- κB can be activated via two distinct NF- κB signal transduction pathways, the so-called canonical and non-canonical pathways, play a key role in a wide range of inflammatory diseases and various types of cancer. The development of pharmacological compounds that selectively inhibit NF- κB activity and therefore would be beneficial for immunotherapy of transplantation, autoimmune and allergic diseases, as well as an adjuvant approach in patients treated with chemotherapy for cancer.[4]

The non-canonical pathway also appears to have an immunoregulatory role in addition to its role in developmental biology [5-8]. IKK α□ negatively regulates inflammation in macrophages via either control of IKK β□ activity [9] or by accelerating the turnover of pro-inflammatory RelA and c- Rel-containing dimers and their removal from pro-inflammatory gene promoters [10]. In addition, NIK has a role in the development of regulatory T cells [11]. Furthermore, authors found that selective knock-down of the noncanonical pathway using siRNA for IKK α or NIK in dendritic cells (DC) resulted in increased pro-inflammatory cytokine production [12], suggesting that a similar negative regulation also takes place in DC. Recent literature demonstrates that the non-canonical NF- κB pathway is also required for other regulatory functions in these cells, including the induction of Treg and the immunoregulatory enzyme indoleamine-2,3-dioxygenase (IDO) [12,13]. Based on these findings it is hypothesized that non-canonical NF- κB signaling is important in the regulation of immune responses [14].

Another mechanism by which transcription of NF-κB responsive genes can be regulated is via modification of histone acetylation by histone acetyltransferases (HATs) and histone deacetylases (HDACs) [15]. Histone acetylation status influences the accessibility of DNA to the transcriptional machinery by changing the folding and functional state of the chromatin fiber [16]. NF- κB interacts with HATs to positively regulate gene expression and with HDACs to negatively regulate transcription of NF-□κB responsive genes [17]. Recently, a novel mechanism of p65 transcriptional regulation was described as pro-inflammatory stimuli activate IKK

α-mediated sumoylation-dependent phosphorylation of PIAS1. This results in the repression of NF- κB - and STAT1-dependent transcriptional responses [18].

These and other regulatory mechanisms are described in great detail in an excellent recent review article [19].

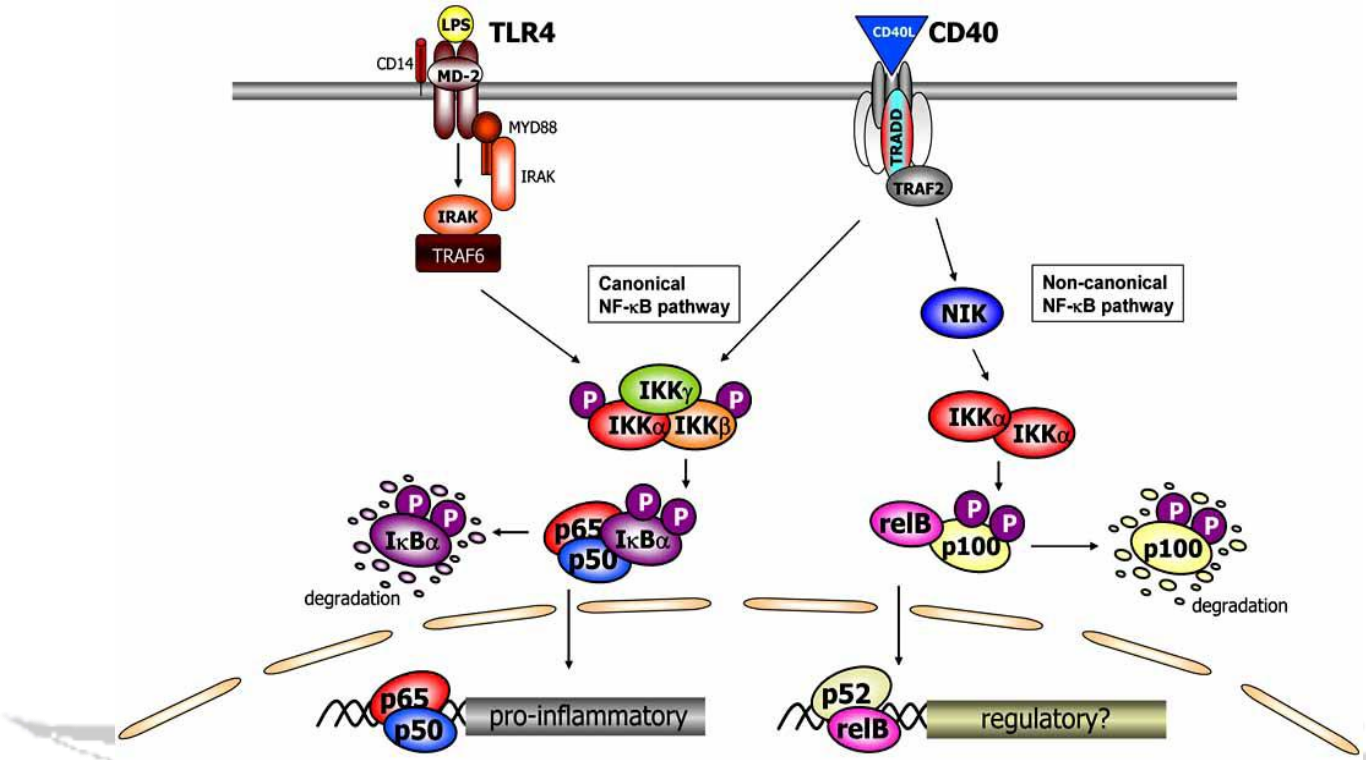

Fig. (4). Schematic representation of the NF- κB signal transduction pathways.

Nuclear factor- κB (NF- κB) can be activated by a multitude of different stimuli, like TNFα, LPS and CD40L. Activation of the canonical (also known as classical) pathway via Toll-like receptor (TLR) or cytokine receptor signaling depends on the IKK complex, which is composed of the kinases IKKα and IKKβ, and the regulatory subunit IKKγ (NEMO). Activated IKK phosphorylates (P) I κB α to induce its degradation by the 26S proteasome, allowing NF- κB dimers (p50-p65) to translocate to the nucleus and bind to DNA to induce NF- κB target gene transcription. Activation of the non-canonical (also known as alternative) pathway is strictly dependent on IKKα homodimers. The target for IKKα homodimers is NF- κB 2/p100, which upon activation of IKKα by NIK is phosphorylated and incompletely degraded into p52, resulting in the release and nuclear translocation of p52-RelB dimers. This pathway can be triggered by the activation of members of the TNF-receptor superfamily such as CD40 (that also induce canonical NF- κB signaling), but not via pattern recognition receptors such as TLRs. [4]

DNA Damage Repair Mechanism

The genomes of all living organisms are constantly subjected to conditions that induce damage to DNA. Some of the damage occurs spontaneously and is the sunlight.On the other hand, radiotherapy or result of normal metabolic processes. For example, deamination of cytosine in DNA can form uracil, which is an aberrant base that must be removed to permit DNA to resume normal transactions, such as during the synthesis of new DNA strands. The formation of uracil is estimated to occur 100-500 times per human cell per day, and is the most common aberrant deamination product in cells [20,21,22,23,24]. Single and double strand DNA breaks are other examples of damage that can occur spontaneously [25]. These breaks form during intermediate steps in DNA replication as well as recombination, or due to the action of reactive oxygen species (ROS) generated by aerobic metabolic pathways. Aside from DNA strand breaks, a large variety of base damage can occur after exposure to ROS [26]. Errors in DNA replication can sometimes lead to insertion of the wrong base and thus result in nucleotide mismatches. DNA strand breaks, as well as inappropriate uracil moieties or base pair mismatches, are usually processed and the DNA mended quickly, thus avoiding adverse biological effects. Cells are also exposed to exogenous agents, chemicals or radiations, which can induce DNA damage. Individuals can be exposed to environmental contaminants or naturally occurring DNA damaging agents, such as radon or and the kinds of damage they induce. Interestingly as

chemotherapeutic agents often target DNA and induce damage [27]. Uracil in DNA cannot only form spontaneously, but also after cytosine in particular is subjected to ionizing radiation exposure [28]. Moreover, ionizing radiation can cause single and double strand breaks in DNA as well, and less frequently base damage. Table 1 lists example of commonly used chemotherapeutic agents that cause DNA damage, directly or indirectly, the types of cancers for which they are employed to eradicate, indicated, representatives of many different categories of chemotherapeutic agent cause DNA damage, and the exact damage induced can be different between groups as well as within the same category of agent. For example, alkylaing agents can cause aberrant methylation of guanines in DNA, and DNA strand cross-links. Chemotherapeutic antibiotics, for example bleomycin, can bind DNA, inhibit DNA replication or transcription, and cause DNA strand breaks.[21]

Table 1. Chemotherapeutic Agents, the Kinds of Cancers for which they are used, and their Mode of Action [29]

Chemotherapeutic Agent	**(Class; Examples)**	**Examples of Cancers Treated Mode of Action/DNA Damage**
Alkylating agents: Nitrogen mustard derivatives (i.e., cyclophosphamide, chlorambucil, melphalan), ethylenimines (i.e., thiotepa), alkylsulfonates (i.e., busulfan), triazenes (i.e., dacarbazine), piperazines (i.e., TFMPP, MCPP, MEOPP, and PFPP, nitrosoureas (i.e., BCNU, CCNU)	Lymphomas, chronic leukemia, multiple myeloma, solid tumors	➢ Adds methyl or other alkyl groups to guanines. ➢ Causes DNA strand cross-links.
Antibiotics: Bleomycin, Dactinomycin, Doxorubicin	Choriocarcinoma, lymphomas, testicular carcinoma, Wilm's tumor, breast cancer	➢ Binds to DNA, inhibits DNA replication, transcription. ➢ DNA strand breaks.
Topoisomerase I and II inhibitors: Irinotecan (Topo I), Etoposide (Topo II)	Colorectal cancers (Irinotecan); Lung cancer (Etoposide)	➢ Effects recombinational repair.
Spindle poisons: Taxanes (paclitaxel and docetaxel)	Breast and lung cancers	➢ Disrupts microtubule function.
Miscellaneous: Cisplatin, Hydroxyurea	Testicular, lung and ovarian cancer (Cisplatin); Chronic and acute leukemias (Hydroxyurea)	➢ Cisplatin: intra-strand, inter-strand DNA crosslinks. ➢ Hydroxyurea: inhibits ribonucleotide reductase, alters deoxyribonucleotide pools, delays cell cycle progression, causes DNA degradation.

A comprehensive list and description of commonly used chemotherapeutic drugs can be found in reference [29].

Unique Biology of Mcl-1

This suggests that Mcl-1 can play an early role in

Mcl-1 plays a critical pro-survival role in the maintenance of both normal and malignant tissue. Mcl-1 protein levels can be both rapidly induced and rapidly lost in response to different cellular events: survival factors can trigger the rapid induction of Mcl-1 transcription; and DNA damage leads to the rapid elimination of Mcl-1 protein levels. response to signals directing either cell survival or cell death. Deregulation of pathways regulating Mcl-1 that result in its over expression likely contribute to a cell's inability to properly respond to death signals possibly leading to cell immortalization & tumorigenic conversion.[30]

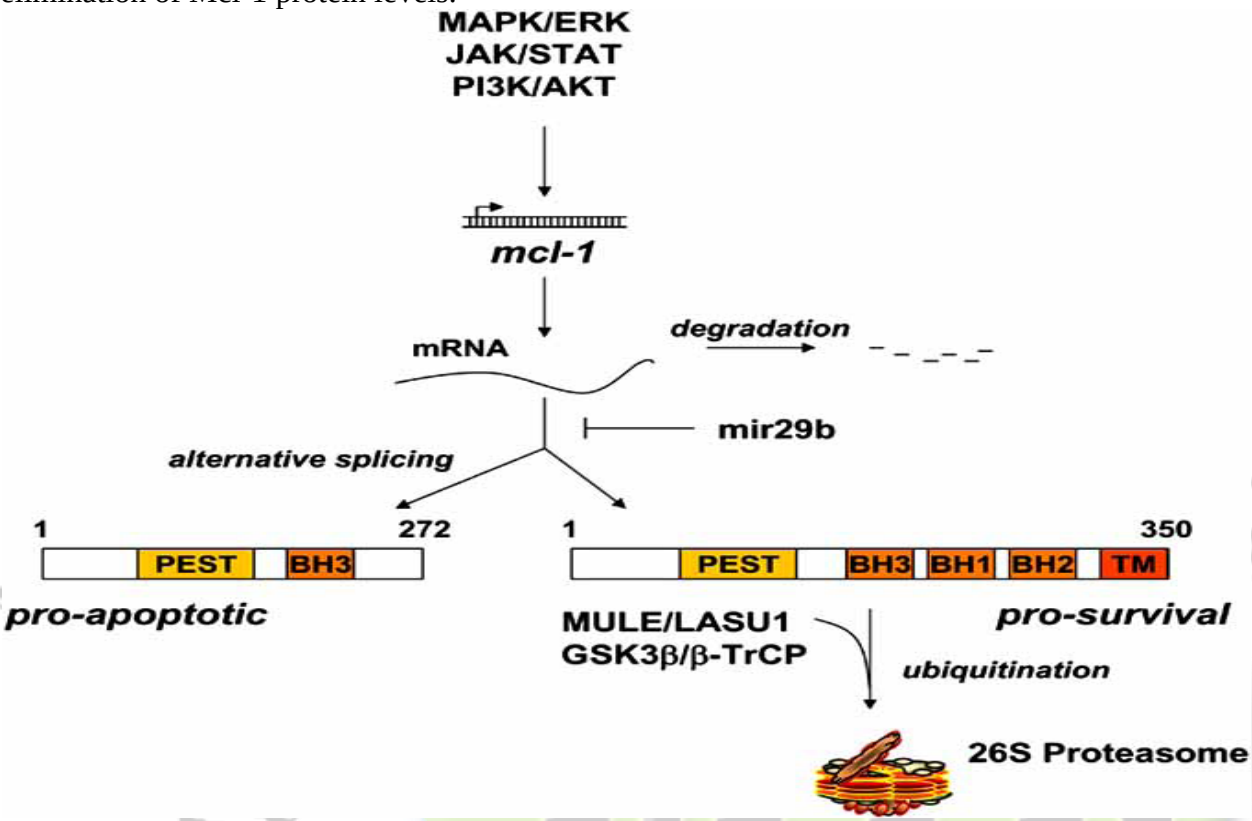

Fig. (5). Mcl-1 is regulated at transcriptional, post-transcriptional, and post-translational levels. Several extra-cellular stimuli can trigger the transcriptional induction of Mcl-1. Mcl-1 mRNA has a short half life and is regulated by micro RNA mir-29b. Alternative splicing can lead to a C-terminally truncated product that is pro-apoptotic. Mcl-1 protein levels are regulated by ubiquity in mediated degradation through both MULE/LASU1 and GSK-3β□β-TrCP.[30]

Oncogenic and Tumor Suppressive Activities Of E2F

Deregulation of E2F transcriptional activity as a result of alterations in the p16INK4a-cyclin D1-Rb pathway is a hallmark of human cancer. E2F is a family of related factors that controls the expression of genes important for cell cycle progression as well as other processes such as apoptosis, DNA repair, and differentiation. Some E2F family members are associated with the activation of transcription and the promotion of proliferation while others are implicated in repressing transcription and inhibiting cell growth. It is now becoming clear however, that this view of the E2F family is overly simplistic and that the role of a given E2F in regulating transcription and cell growth is highly dependent on context. This complexity is also evident when analyzing how perturbations in E2F modulate tumor development. As expected, some E2F family members are found to be critical for mediating the oncogenic effects of Rb loss. On the other hand, several E2Fs have tumor suppressive properties in mouse models and this appears to be reflected in some human cancers with decreased E2F expression. Surprisingly, tumor suppressive activity is not associated with the repressor E2Fs but instead is associated with the same E2Fs shown to have oncogenic activities. For example, deregulated E2F1 expression can either promote or inhibit tumorigenesis depending on the nature of the other oncogenic mutations that are present. Thus, the ability of some E2F family members to behave as both oncogene and tumor suppressor gene can be reconciled by putting E2F into context.[31]

Fig. (6). Context-dependent modulation of tumor development by E2F1. Loss of p53 or ARF function cooperates with E2F1 overexpression to enhance tumorigenesis. On the other hand, E2F1 overexpression suppresses Ras-driven tumorigenesis. Inactivation of *E2f1* decreases tumorigenesis in *Rb*+/- mice and Em Myc transgenic mice. In contrast, the absence of E2F1 promotes tumor development in K5 Myc transgenic mice. Inactivation of both *E2f1* and *E2f2* enhances tumor development mediated by the Bcr-Abl oncogene, and this is shown to be a non-cell autonomous effect.[31]

Role of Chelates In The Treatment Of Cancer

Chelates are inorganic agents that have good clinical effects in treatment of various types of cancer as cytotoxic agent. It is thought that chelates are deactivating either the carcinogenic metal or the enzymes necessary for the rapid growth of both healthy and malignant cells. Various chelates based on ruthenium, copper, zinc, organocobalt, gold, platinum, palladium, cobalt, nikel, and iron are reported as cytotoxic agents. The use of monoclonal antibodies labeled with radioactive metals in treatment of malignancies is an evolving field.[32]

Redox pathways in cancer

Most cellular pathways are affected by oxidation/reduction reactions and thus it is not surprising that an imbalance in cellular redox homeostasis for example, due to the occurrence of oxidative or nitrosative stress, is associated with several disease pathophysiologies including malignancies. The article by Grek and Tew discusses the complex interplay of extracellular and intracellular redox reactions which, when disrupted, have many consequences on cellular dynamics. Moreover, disruption of the reactions has the potential of altering the efficacious response of prospective therapeutic entities including mechanisms related to the development of drug resistance. The cellular origin of aberrant reactive species in tumor tissue has the potential of developing more relevant therapies to counter tumorigenesis and metastasis and to develop tumor-specific therapeutics. The role of oxidative stress in metastasis and tumor progression is complex and involves a number of factors including cell type, cellular microenvironment, and free radical type and compartmentalization. Tumor survival depends on a number of processes involving proliferation, motility, apoptosis and senescence, all of which are influenced by changes in redox metabolism. Complexity lies in the fact that individual cancers may be characterized by different redox-based signaling mechanisms. However, as new approaches emerge, e.g. the discrete roles of extracellular vs. intracellular redox state; the importance of non-radicals in redox metabolism; the recognition of the impact of tumor microenvironment on metastasis, the utility of targeted redox-modulating therapeutics may flourish. [33]

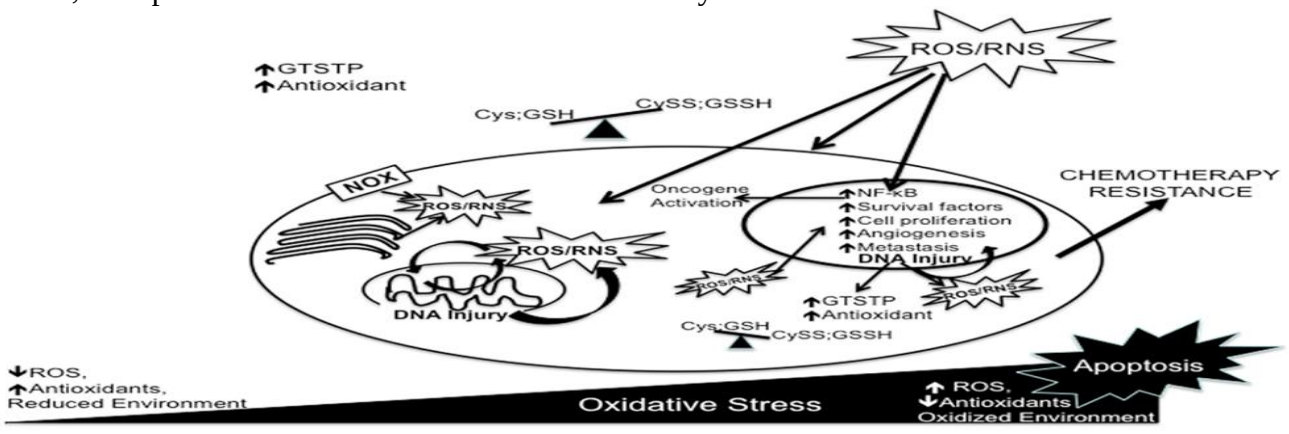

Figure (7). Accumulation of reactive oxygen species (ROS) and/or reactive nitrogen species (RNS), derived either endogenously or exogenously, results in oxidative stress. Disruption of thiol and non-radical circuits may also result in oxidative stress. The extent of this stress will either result in lethal damage and apoptosis or in cell adaptation. In cancer cells chronic oxidative stress activates redox sensitive transcription factors and signaling pathways that act to increase the expression of antioxidants, increase expression of survival factors as well inhibit the expression of pro-apoptotic pathways. ROS/RNS induced DNA injury promotes genomic instability and further provides opportunity to adapt to oxidative stress. Cancer progression occurs via the regulation of redox dependent expression of genes that play roles in proliferation, senescence evasion, metastasis, and angiogenesis. These features in association with the disruption in antioxidant profile may contribute to altered drug sensitivity and chemotherapy resistance.

Definition of abbreviations: NOX, NADPH oxidase; nuclear factor-κB; NF-κB; Cys, cysteine; Cyss; cystine; GSH, glutathione; GSSH, glutathione disulfide, GSTP, glutathione-*S*transferase P.[33]

Hedgehog pathway inhibitors: Novel receptor antagonists for cancer therapy:

The Hh pathway is developmentally important, and represents a novel opportunity for cancer therapy. The Hh pathway is mutationally activated in certain cancer types, such as BCC, and has been demonstrated to be important in tumor/ stromal interactions and, in some tumor types, in the maintenance of cancer stem cells.

Targeting the Hh pathway offers a novel therapeutic approach with the potential to broadly impact multiple cancers through effects on both tumor/strostromal interactions and cancer stem cell maintenance. The progression of several exciting new drugs currently under clinical evaluation seems likely to resolve the question of the true significance of the Hh pathway in cancer biology. [34]

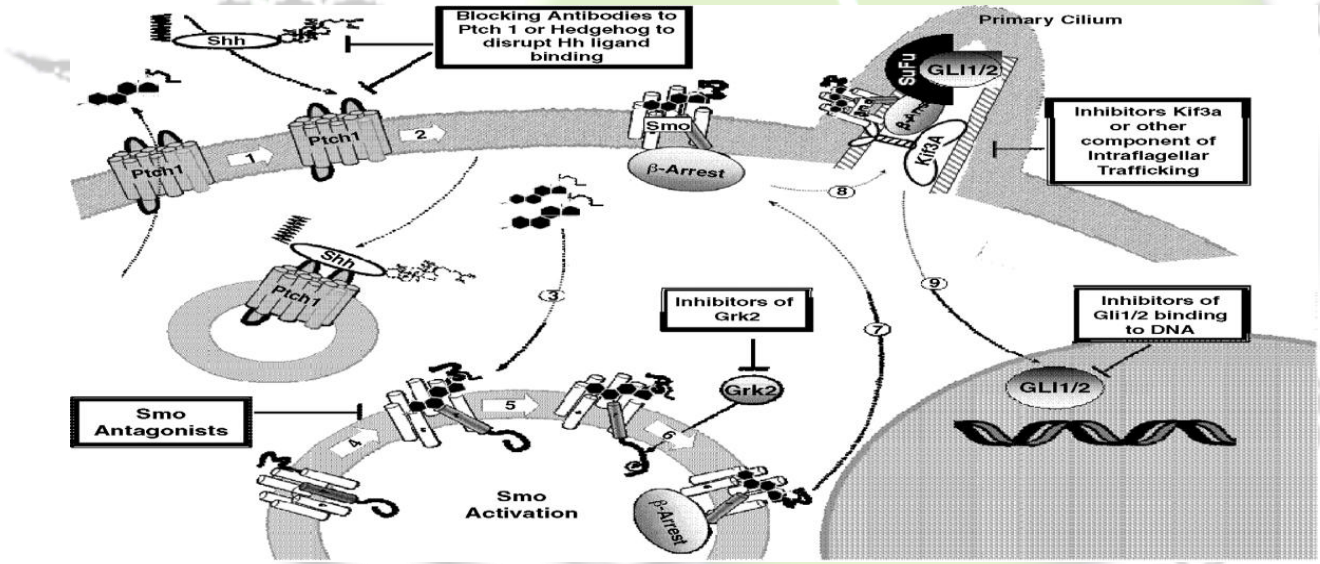

Figure (8). The hedgehog pathway and potentials for therapeutic intervention. In the absence of Hh ligand stimulation, Ptch inhibits Smo activation, apparently through the cellular translocation of a sterol second messenger that acts either as an endogenous Smo agonist (represented here) or antagonist. (1) Upon Hh binding, Ptch is internalized (2) and possibly degraded. The small molecule accumulates (3), whereupon it can bind Smo (4), probably inducing a shift in the helical transmembrane-7 domain (5). This binding opens the contiguous intracellular domain to phosphorylation by Grk2 (6) triggering association with b-arrestin. Once activated, the complex translocates to the base of the primary cilium (7) where it associates with an intraflagellar transport (IFT) protein complex including the kinesin Kif3a (8) and shuttles along the ciliary microtubules to accumulate in the ciliary cell membrane. In the cilium, the activated Smo encounters Sufu sequestering the Gli1 and Gli2 transcription factors, and triggers their release enabling their translocation to the nucleus (9). In the nucleus, Gli1/2 activate the Hh-responsive genes including genes responsible for developmental patterning and maintenance of pluripotency (e.g. BMP4, Bmi1), cell growth and survival (Cyclin D1, N-Myc) and components of the Hh pathway components (Gli1, Ptch). Avenues to target the Hh pathway include demonstrated approaches (blocking antibodies to the hedgehog ligands and Smo antagonists) and theoretical approaches (blocking antibody to Ptch; inhibitors of Kif3a or Grk2 catalytic activity; inhibitors of Gli1/2 DNA binding).[34]

Anti cancer activity of Antimicrobial peptides

Despite recent advances in treatment modalities, cancer remains a major source of morbidity & mortality throughout the world. A growing no. of studies have shown that some of the cationic antimicrobial peptides (AMPs), which are toxic to bacteria but not normal mammalian cells, exhibit a broad spectrum peptides (AMPs) is electrostatic attraction between the negatively charged components of bacterial and cancer cells & the positively charged AMP causes selective disruption of bacterial & cancer cell membranes respectively.[35]

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