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Cancer Stem Cells, Wnt, Hedgehog and Notch Signaling, the Role of Dietary Phytochemicals: New Insights for Cancer Therapy

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Abstract

Therapy resistance and relapse is the worst prognostic outcome of cancer and is attributed to the presence of cancer stem cells in the tumor mass. Cancer stem cells survive the cytotoxic effects of commonly used chemotherapeutic drugs and radiation which targets and eradicates non cancer stem cells reducing the tumor bulk but is unable to stop tumor recurrence. Cancer stem cells re-initiate the evolutionary conserved embryonic signaling pathways such as Wnt, Hedgehog and Notch thereby endowing themselves with properties of pluripotency, self renewal and maintenance, activate DNA damage repair systems opposing effects of radiation and express energy driven drug efflux pumps expelling chemothepeutic drugs. Development of new therapeutic strategies aiming self sustained, self renewed, apoptosis surviving, aberrantly proliferating therapy resistant cancer stem cells and minimizing long term side effects may provide cure and better 5 year survival rate is the ultimate goal which instigate screening, designing and understanding the roles of different physiologically tolerant compounds that can affect the stem cell program. Phytochemicals like Vitamin D3, Epigallocatechin-3-gallate, Sulforaphanes, Genistein, Curcumin, Cyclopamine, Retinoic acid, Resveratrol, Parthenolide and Quercetin often found in our diet are known for their anti inflammatory and anti oxidative properties and are being studied for their anti cancer stem cell activities. Recent revelation showing inhibition of self renewal and proliferation signaling and promotion of apoptosis in cancer stem cells by these bioactive compounds has prompted the need of more advanced research to comprehend the molecular mechanisms involved, ascertaining accurate dosage and nullify negative drug interactions if any providing new insights in the field of cancer prevention by dietary phytochemicals.

Background

Cancer or neoplasia is the major killer in the 21st century. Though human kind has been able to achieve great heights in the field of medicine and has unfolded the scientific aspects of nearly all human diseases yet the development of a potent drug against cancer is due for long which gets reflected in the GLOBACON 2008 where about 12.7 million cancer patients and 7.6 million deaths were estimated to have occurred in the year 2008 worldwide [1]. The human body consists of more than 10^{14} number of cells where each cell behaves socially with others and forms a well regulated and organized system dedicated to pass on copies of their genes through germ cells and accept self sacrifice ultimately but substantial numbers of mutations and epigenetic alterations within a cell may change its behavioural pattern making the cell neoplasmic, endowed with selfish traits, enabling them to survive and proliferate more vigorously and expand their progeny to finally jeopardize the system. Malignant cancer cells in defiance to normal restraints of cellular growth escape apoptosis and proliferate in to the space occupied by other cells to form a tumor and often penetrate blood or lymphatic vessels and colonize at a distant site to form a secondary tumor, a process called metastasis [2]. During recent times the common modes of treatment for neoplasia includes surgery, chemotherapy and radiotherapy with the intent to control the disease and not always with a curative objective due to frequent cases of recurrence. Surgery can reduce the tumor burden in cases of solid cancers and can facilitate the radical cure whichever is possible with the aid of chemoradiation with radical dose but sometimes surgery is not suitable for some specific cancers like small cell carcinoma and some other non solid malignancies like leukemia, multiple myeloma, etc. and also curative surgery has limitations when disease is over burdened with distal metastasis at multiple inaccessible sites. Commonly used cytotoxic chemotherapeutic drugs and associated adjuvant therapies does not contribute much to the cure and according to a statistical study by Morgan et al. the 5 year survival in adults is less than 3% [3]. Radiation therapy done to kill cancer cells by damaging their DNA though considered best as a non surgical method to cure localized cancer yet recent studies show that radiotherapy done to treat childhood cancer increases greater risks for developing a second cancer in the later stages of life [4]. In the last few decades poor prognosis of the disease, therapy resistance and recurrence of neoplasia has been attributed to cancer stem cells emerging from the concept that a tumor mass is a heterogeneous population consisting of cancer cells having varying function and structure, in which minor subset or subsets of undifferentiated, slow dividing cells having the property of self renewal and unlimited proliferation which permit them to form tumors more efficiently compared to other cells in the same tumor mass. The presence of cancer stem cells also known as tumor initiating cells were first isolated in acute myeloid leukimea and later in solid cancers like breast, brain, lung, prostate, colon, melanoma, liver and pancreatic neoplasias [5,6]. Distant malignancy after metastasis has been attributed to the gain of these 'stem like traits' by the cancer cells undergoing epithelial mesenchymal transition, a latent developmental strategy taken up by cancer cells to migrate and invade [7]. Chemoresistance and relapse of the disease after shrinkage of the initial neoplastic mass by use of common modes of drug therapy by aberrant stimulation of key developmental signaling cascades, principally Wnt, Hedgehog and Notch has been ascribed to cancer stem cells [8,9]. Chemotherapeutic drugs and radiation therapy are both non specifically cytotoxic to both normal and cancer cells as they are targeted to damage the DNA and cause cell cycle arrest (Figure 1), but cancer stem cells are chemo and radio resistant due to presence of

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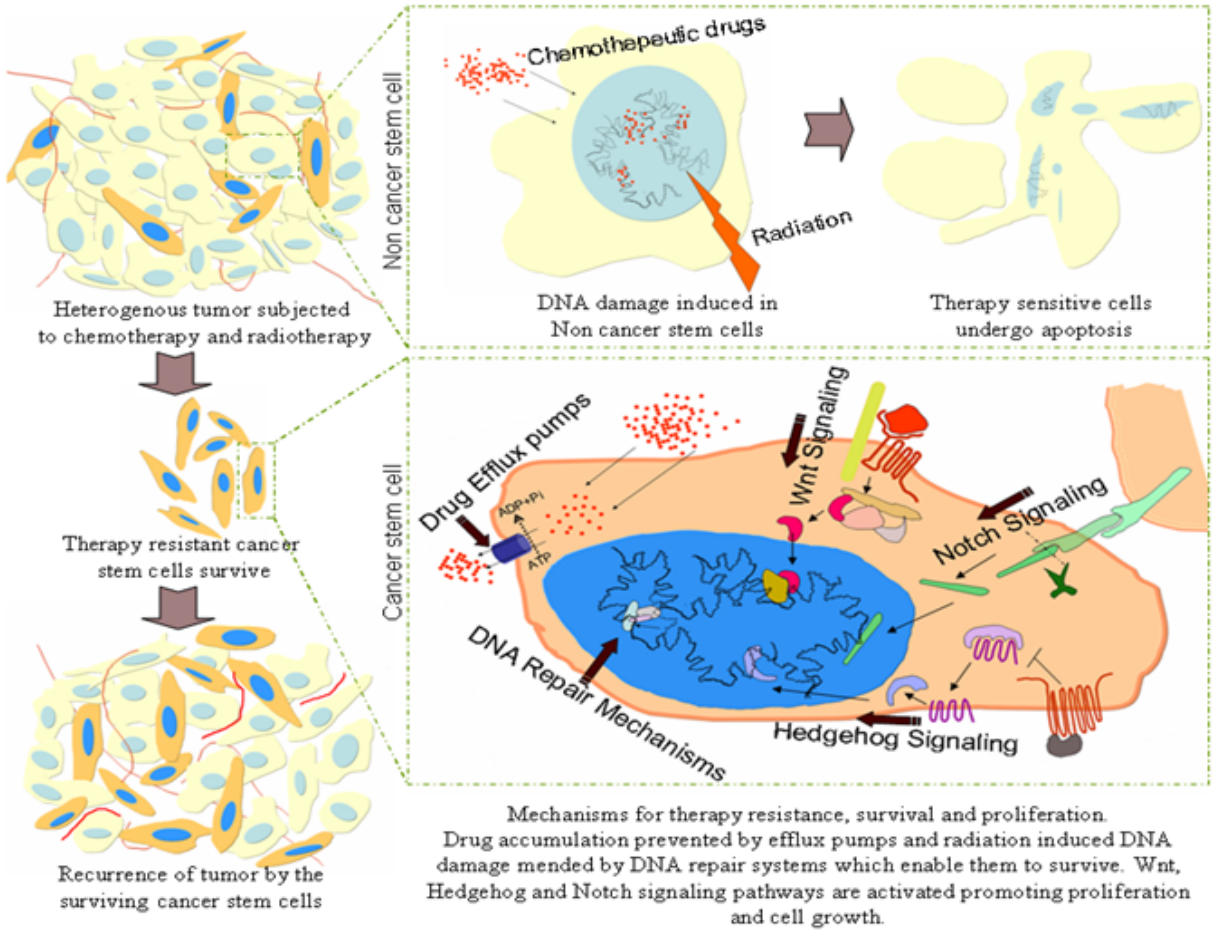

Figure 1: Chemotherapy and radiotherapy induced response of cancer stem cells vis-à-vis non cancer stem cells

extensive DNA repair mechanisms, slow doubling rate and presence of drug efflux pumps. Radiation induced DNA damage to kill cancer cells in some studies have been found to increase the number of cancer stem cells due to presence of effective levels of checkpoint kinases 1/2 (Chk1/2 kinases) which may be due to selection pressure and other reports indicate that the gain of chemoresistance is due to activation of AKT pathway or IL-4 receptor stimulation, increased activity of Aldehyde Dehydrogenase 1 (ALDH1) and most importantly due to presence of energy driven ATP-binding cassette (ABC) transporters, including Multidrug Resistance Transporter 1 (MDR1) and Breast Cancer Resistance Protein (BCRP) which enables the cancer stem cell to effuse drugs like paclitaxel, imatinib mesylate, topotecan and methotrexate [10,11]. Therefore, better prognosis of the disease demands development of drugs that can preferentially kill cancer stem cells specifically. Screening, identification and designing of anti cancer stem cell specific drugs was limited by the rarity of CSCs in cell lines and tumors, their spontaneous differentiation and complicated clonogenic functional assays was surmounted from the interpretation of the findings that cells undergoing epithelial mesenchymal transitions up regulate genes responsible for proliferation and self renewal, thereby becoming cancer stem cells [7] and paved the way to generate sufficient numbers of breast cancer stem cells by inducing EMT activating genes in cancer cells and consequently enabling high throughput screening of more than 16,000 compounds and detection of salinomycin that preferentially kills breast cancer stem cells as compared to some other chemotherapeutic drugs currently in use [12]. Salinomycin, an effective anti microbial agent used to treat poultry diseases, was found to target cancer stem cells in different types of human cancers, including gastric cancer, lung adenocarcinoma , osteosarcoma , colorectal cancer, Squamous Cell Carcinoma (SCC), and prostate , as well as shows more profound effect when used in combination with other conventional cytotoxic drugs by inducing apoptosis and differentiation, inhibiting oxidative phosphorylation and Wnt signaling pathway, interfering with drug efflux pumps and K+ channels but its high toxicity in mammalian system and its acute destructive side effects as evidenced in clinical case studies and in vivo experiments put the application of the drug in question [13]. Genes that are expressed in embryonic stem cells like Wnt β-catenin, Hedgehog and Notch which are evolutionary conserved are often found to be incongruously up regulated in cancer [14] and their inhibitors effectively eradicating cancer stem cells [15] stipulate them as potential therapeutic targets. It has been estimated that nearly one third of all cancer deaths can be prevented by changing lifestyle and nutrition [16] and as dietary phytochemicals which are plant derived non nutritive compounds are well documented for their pleiotropic actions in suppressing tumor initiation and growth in a variety of cancers including leukemia, prostrate, breast, brain, melanoma and pancreatic [17] can act as promising anti cancer stem cell agents as they are well tolerated by the human system and can target the Wnt, Hedgehog and Notch embryonic pathways and tackle the problem of multi drug resistance.

Wnt, Hedgehog and Notch; 'The Three Musketeers' of Cancer Stem Cell Signaling

Wnt β-catenin signaling controls many aspects of development in animals. This canonical wnt signaling is activated when extracellular wnt ligand bind to Frizzled family of cell surface receptor protein and a low density receptor lipoprotein (LRP). In the absence of wnt ligand β-catenin remains bound to axin and Adenomatous Polyposis Coli (APC) proteins and gets phosphorylated by Casein Kinase I alpha (CKIα) and Glycogen Synthase Kinase 3 beta (GSK3β) and undergoes polyubiquitination followed by proteosome mediated degradation. Binding of Wnt to Frizzled and LRP promote their clustering and formation of Frizzled-Dishevelled and LRP-Axin-FRAT complexes which inactivates GSK3β via Dishevelled (Dvl) and stabilizes catenin. β-catenin translocates to the nucleus and binds to T-Cell Factor/ Lymphoid Enhancer Factor (TCF/LEF) and other coactivators inducing Wnt responsive genes DKK1, WISP1, MYC, among others promoting cellular proliferation and growth [2,18]. Similar to wnt ligands are Secreted Hedgehog (Hh) signaling molecules like Sonic (SHh), Indian (IHh), and Desert (DHh) are found in mammals. Mature Hh proteins are ligands of Patched (Ptch) transmembrane receptors. In absence of ligand the Ptch inhibits the activation of Smoothened (Smo) proteins and GLI family of zinc finger proteins form complexes with SuFu (suppressor of fused homolog). When Hh ligand binds to Ptch receptor then Smo localizes to the plasma membrane and prevents degradation of GLI. GLI translocates to the nucleus and activates transcription of Hh responsive developmental genes [2,18]. Signaling between two adjacent cells occur via binding of notch and delta which regulate cell fate decision. The cytoplasmic tail of a single pass transmembrane protein notch is cleaved by γ-secretase complex when its extracellular domain binds to the ligand delta attached to an adjacent cell. The cytoplasmic tail called Notch Intracellular Domain (NICD) translocates to the nucleus and activates notch responsive genes which regulate renewal and pattern formation of tissues [2,18].

Potent Phytochemicals that can Target Cancer Stem Cells

Vitamin D3

Epidemiological findings indicate that vitamin D3 reduces incidence of breast, prostrate, and colon cancers in human by inducing apoptosis and cell cycle arrest. The active form of vitamin D3 (1,25 dihydroxyvitamin D3) mediates anticancer activities by acting on the Wnt β-catenin signaling as evidenced in colon carcinoma where the wnt signaling ligands DKK1 and DKK4 are upregulated and down regulated in contrast to untreated tumors. β-catenin responsive genes such as c-myc, peroxisome proliferators-activator receptor, Tcf-1 and CD44 are also shown to be down regulated in colon cancer cells forcing them to differentiate and loose self renewal ability [19-21].

Epigallocatechin-3-gallate (EGCG)

Green tea, a popular beverage consumed worldwide contains variety of phenolic catechins, among which Epigallocatechin-3-gallate (EGCG) is most abundant and has been studied intensively for its chemopreventive actions against many cancer types and its consumption is associated with lower risk of neoplasias as documented in epidemiological studies. Green tea extracts inactivated P-glycoprotein, an energy dependent drug efflux pump of the ABCG2 family in Chinese hamster ovary cells and prevented the accumulation of rhodamine123 dye. Chemotherapeutic drugs, Doxorubicin and Vinblastine when used in combination with EGCG, more enhanced and effective anticancer activity was achieved probably due to longer stay of the drugs inside the cells to induce cell cycle arrest. HBP1, a suppressor of Wnt signaling pathway is stabilized by EGCG and thereby reduce the proliferation and invasiveness of breast cancer by suppressing the Wnt signaling. EGCG can also restrain the activation of Akt in different colon cancer cell lines and mouse models. Studies on transgenic mouse model having a mutated APC gene show that this compound hinders the nuclear transport of β-catenin. EGCG can also hamper the NF-κB signaling by preventing its activation. Bmi1 protein, one of the proteins of the Polycomb Group Repressive Complex 1 (PRC 1) is expressed by cancer stem cells and is accompanied with decrease in tumor suppressor gene expression is reduced by EGCG treatment leading to decrease in cell cycle dependent kinase 1, 2 & 4 and cyclin D1 [17,19-21].

Sulforaphanes

Isothicyanates like sulforaphanes found in cruciferous vegetables like broccoli and broccoli sprouts are glucosinolate derived organosulphur compounds show promise as a potent anticancer stem cell agent as they are able to suppress mammosphere formation in breast carcinoma cell lines MCF7 and SUM159. Sulphoraphane target the wnt signaling by down regulating β-catenin as evidenced in cervical cancer cell line HeLa, hepatocarcinoma cell line HepG2 and suppress expression of Wnt ligand (Wnt-9a) in APC gene mutated mouse models. In ovarian, prostate and colorectal cancers it has been found to suppress the Akt pathway. The antitumor effects mediated by sulphoraphane include regulation of JNK, HIF-1a, ER, Fas signaling pathways leading to cell cycle arrest and apoptosis, inhibiting EMT related proteins and Histone Deacetylase (HDAC) and targeting anti-oxidant transcription factor Nrf2. Interference with TRAIL (TNF-related apoptosis inducing ligand) activated NF-κB signaling resulted in loss of resistance to TRAIL by pancreatic tumor initiating cells, downregulation of NF-κB signaling in prostate and colon cancer has also been established [17,19-21].

Genistein

Genistein, the predominant isoflvone found in soybean is held responsible for lower incidence of breast and prostate cancers in Asian compared to Western countries. Down regulation of sfrp2 (secreted-frizzled-related protein 2), an antagonist of Wnt ligands is often associated with breast cancer. Gene microarray technique used to conduct a genome wide expression profiling of rat mammary epithelial cells showed that lifetime dietary consumption of genistein inhibited Wnt5a & notch 2 expression and enhanced the expression of sfrp2 thereby suppressing the wnt signaling directly and indirectly by restoring the antagonistic regulation respectively. Inhibitory effect of genistein has also been found in Chronic Myelogenous Leukimea (CML) patients where tyrosine kinase activity remains altered in hematopoietic cells. This isoflavone is able to reduce the self renewal more in cancer stem cells compared to normal hematopoietic stem cells. Self renewal and proliferation mediating protein Akt remain inactive due to prevention of their phosphorylation and induced expression of GSK3β leading to phosphorylation and consequent degradation of β-catenin are also achieved by genistein. Genistein suppress the NF-κB signaling by inhibiting the notch signaling in pancreatic cancer stem cells followed by cell cycle arrest and apoptosis has also been reported [17,19-21].

Curcumin

The polyphenol curcumin is obtained as a yellow crystalline powder from turmeric, used to provide flavor and color in Asian cuisines is

long known for its anti inflammatory and anti oxidative properties. Most of its chemopreventive action is due to inhibition of NF-κB and mTOR signaling pathways. Curcumin target cancer stem cells by suppressing the mammosphere forming ability and by inhibiting the transcriptional activity of Wnt β-catenin signaling as evidenced in gastric, colon and intestinal carcinoma cell lines. Wnt β-catenin signaling is suppressed (Figure 2) by the down regulation of frizzled-1 wnt receptors by caspase mediated cleavage of β-catenin in HCT111 intestinal cancer cells. Inactivation of notch signaling by curcumin by down regulating notch1 mRNA levels and also in combination with piperine, another dietary polyphenol derived from black and long peppers as evidenced by inhibition of mammosphere formation has been reported. Curcumin can also target the Hedgehog (Hh) pathway observed in mouse colon adenocarcinoma, pancreatic, brain and prostate cancers. Curcumin is also able to sensitize drug resistant cells to common chemotherapy and can inhibit the activity of ABCG2 drug efflux pump [17,19-21].

Cyclopamine

Corn lily (*Veratrum californicum*) derived phytochemical cyclopamine inhibits the Hedgehog (Hh) signaling pathway by inhibiting the activation of the Smothened (smo) protein. Cyclopamine has been found to be effective against cancer stem cells in pancreatic, breast and multiple myeloma where it has suppressed sphere formation and proliferation. In medulloblastoma mouse models, cyclopamine also reduced tumor burden by reducing cancer stem cells, promoting their differentiation and blocking proliferation [19].

Retinoic acid (RA)

Retinoic acid (RA), the active form of vitamin A, fat soluble micronutrient found in carrots, broccoli and liver can promote differentiation of stem cells as found in Acute Promyelocytic Leukemic (APL) patients where it has induced transformation of promyelocytic leukemic cells to mature neutrophills. RA directly interacts with sox3, transcription factor and induces differentiation in embryonal carcinoma cells. It reduces pluripotency and abolishes tumorigenicity forcing the embryonic carcinoma cells to undergo G1 cell cycle arrest [19].

Resveratrol

Resveratrol, a stilbene obtained from grapes, berries and peanuts and also found in red wine has suppressive effects on various carcinoma animal models and carcinoma cell lines. Resveratrol consumption from grapes shows a negative correlation with breast cancer risk and has been reported to inhibit progression of lung cancer. The anti cancer stem cell activity of resveratrol has been attributed to its ability to block the notch signaling pathway as evidenced in acute lymphoblastic leukemia cells where the notch-1 protein expression was decreased.

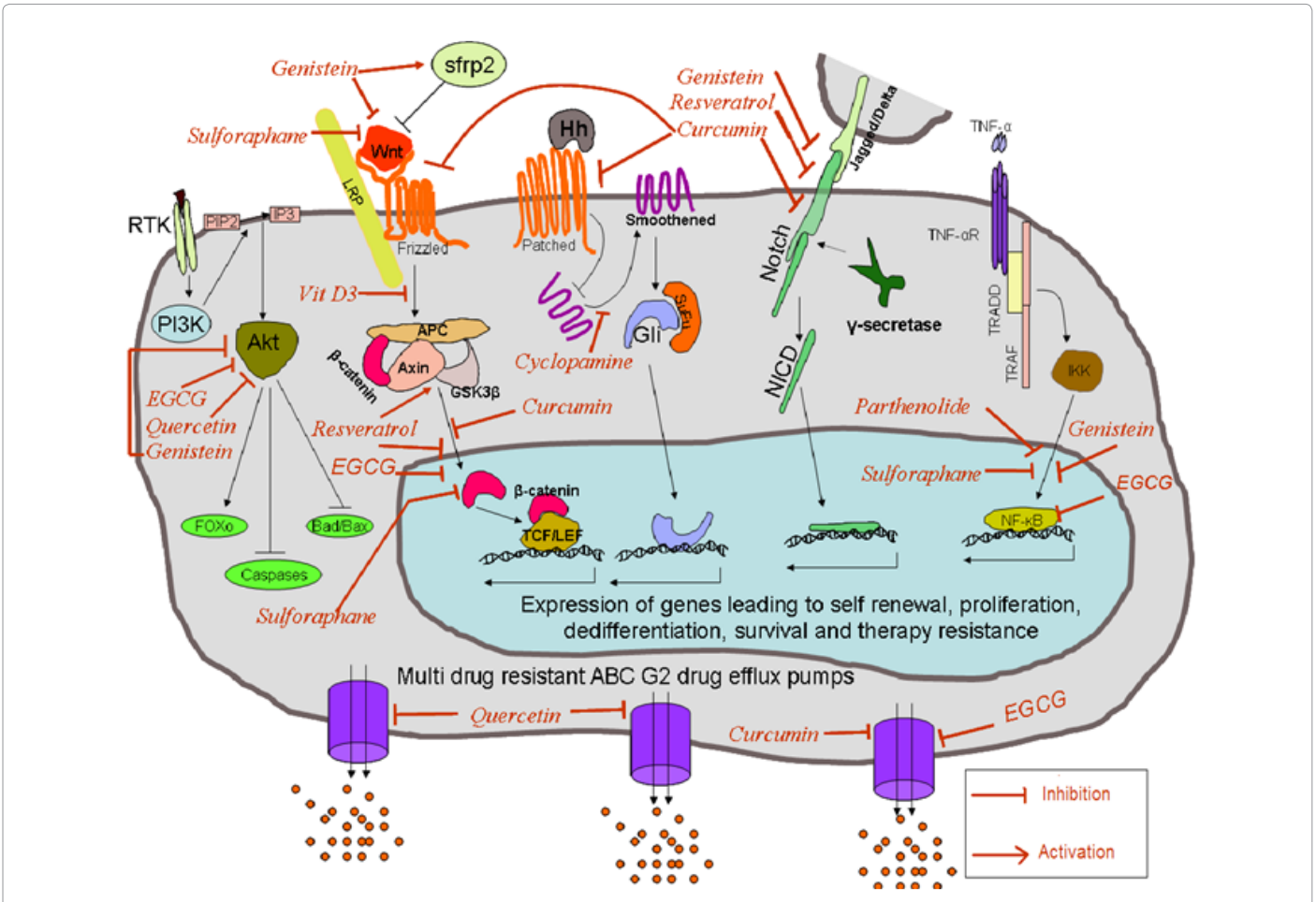

Figure 2: Effect of phytochemicals on cancer stem cells: Names of phytochemicals are in red. The phytochemicals suppress Akt/PI3K, Wnt- β-catenin, Hedgehog, Notch and NF- κB signaling pathways and inhibit the drug efflux pumps

Recent studies with the compound indicate its inhibitory effects on Akt and wnt signaling pathways. It affects the Wnt signaling by inhibiting nuclear localization of β-catenin in colon carcinoma cells and activating GSK3β in acute lymphoblastic leukemia cells [17,19,21].

Parthenolide

Fever few plant extract parthenolide can target Acute Myelogenous Leukemia (AML) stem cells more specifically leaving normal hematopietic stem cells unaffected by increasing Reactive Oxygen Species (ROS), inhibiting NF-κB signaling and p53 mediated apoptosis. It attacks breast cancer stem cells and suppresses mammosphere formation in vitro by altering NF-κB signaling pathway [17,19,21].

Quercetin

Apple, broccoli and onion contains a flavonoid Quercetin shows anti-mutagenic, anti-oxidative, and anti-proliferative effects and regulates several signaling pathways, cell cycle and apoptosis and is known for its anti cancer activities. It can inhibit the PI3K/Akt survival signaling pathway and can sensitize prostate, colon and lung cancer cells to TRAIL induced cytotoxicity by up regulating DR5 and down regulating survivin. This compound can also inhibit MRP1, 4, and 5 ATP Binding Cassette (ABC) drug efflux pumps and in combination with EGCG produces a synergistic effect on inhibiting prostate cancer stem cells [17,19,21].

Conclusion

It was believed that cancer stem cells like normal stem cells remain at the apex of the hierarchy and they asymmetrically divide into more differentiated cells and stem cells, maintaining the pool of stem cells and increasing the number of non stem cells but recent studies show that cancer stem cell model is more stochastic in nature and they do not follow the unidirectional hierarchical model as observed in normal stem cells. There is always a non-zero probability of a non cancer stem cell to dedifferentiate into a cancer stem cell. Therapy done to kill these cancer stem cells specifically leaving non cancer stem cells unharmed may not result in good prognosis as they can dedifferentiate and repopulate the tumor by up regulating transcription factors inducing pluripotency like oct4, Nanog, Klf4 and sox2 gaining stemness either by themselves or via signals received from the microenvironment [22,23]. The plastic nature of the cancer stem cells hold great implication in the development of therapeutic approaches which must be directed not only to the stem cells but also to other non stem cells in the tumor bulk in hope of eradication of disease and cure. Nutrigenomic, nutriproteomic and nutrimetabolomic studies helped in understanding of the roles of low toxic phytochemicals obtained from common foods in prevention of cancer by blocking proliferation, invasion, metastasis, angiogenesis, inflammation, immortality mutation, promoting apoptosis in accordance with inhibiting the survival mechanisms and drug resistant cancer stem cells. Chemoprevention may not be possible by application of single agents and so compounds having pleiotropic actions are often recommended but studies with garlic (*Allium sativum*), ginkgo (*Ginkgo biloba*), echinacea (*Echinacea purpurea*), ginseng (*Panax ginseng*), St John' s wort (*Hypericum perforatum*), and kava (*Piper methysticum*) show undesired effects in cancer treatment. These phytochemicals interact with drug transporter P-gp, and other oxidative enzymes leading to phytokinetic alteration of commonly used chemotherapeutic drugs like cisplatin and methotrexate resulting in their low absorption and high elimination [24]. Such unfavorable drug interactions can do more evil than good in cancer patients stipulating more focus to be directed in unraveling the molecular mechanisms imparted by a phytochemical before being used in alliance with other agents.

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