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REVIEW

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Envisioning the Reversal of Oncogenesis

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ABSTRACT

Cancer, at different stages, is currently treated with conventional methods including chemotherapy, radiotherapy or surgery. These approaches often become ineffective for cancers that have spread aggressively in different parts of the body (metastasis). Hence, researchers have been actively investigating alternative methods to stop cancer-growth (oncogenesis) or even possibly reversing the cancer-growth (regression) without affecting the normal cells. Several approaches are used by scientists ranging from enhancing the immune system (immunotherapy) to genetic manipulations. Prophylactic vaccines are also attempted. An overview of such attempts is presented in this review. Several drugs developed at trial phases, or pre-clinical or exploratory phases are described. Many approaches show a promise of inhibiting oncogenesis, some also in its regression, thereby hinting at a possibility of finding a permanent solution to cancer in future.

Keywords: *Carcinogenesis, oncogene, tumor suppressor gene, cell signaling, cell division, biomarker, target detection, immunotherapy, vaccine, targeted therapy, gene therapy, apoptosis*

INTRODUCTION

Cancer is referred to a group of diseases occurring due to uncontrolled cell division at a focal point (primary), which is either benign (not invading other organs) or malignant (invading nearby sites of the body by metastasis). According to the WHO report in 2013, 8 million people around the world would be dying of cancer this year, with global deaths reaching 13.2 million annually by 2030 [1]. 72% of the cancer deaths occurred in low and middle income countries, due to delays in diagnosis and treatment [2]. There are about 200 different cancers that affect the human body [3].

To address the ever increasing problem of cancer, researchers have investigated and identified specific factors (risk factors) that enhance a person's chance of developing certain types of cancer. Cancer risk factors can be (a) Behavioral: like tobacco, alcohol, dietary factors, lack of physical activity, obesity etc. [4], (b) Environmental: UV radiation, secondhand smoke, pesticides and other toxins, (c) Biological: gender, age, ethnicity, etc., (d) Hereditary: specific mutated genes inherited from parents [5].

Treatment for cancer has undergone evolutionary changes as more research to understand the intrinsic biological processes are being performed. Of late, most of the treatment mechanisms are effective for cancers diagnosed at early stages, but are ineffective for cancers diagnosed at later stages (metastasized). Conventional treatments include combinations of surgery, chemotherapy and radiotherapy. Newer targeted therapies have been devised since the late 1990's for treating specific forms of cancer. Personalized therapy-combinations have also come up as a new arsenal in modern cancer treatment [6, 7]. Other methods of treatment such as lasers [8], photodynamic therapy (PDT) [9], immunotherapy [10, 11], hormone treatment, and angiogenesis inhibitors [12] are also used, but they are not effective in controlling metastatic cancer. Most of them, in the final stages of the disease, are aimed at relieving the symptoms of cancer and improving the quality of the patient's life (palliative care).

Since cancer is the resultant of a genetic mutation, translocation or alteration of the copy number of certain exons

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of chromosomal DNA, the ideal treatment would be to correct the problem at the genetic level. Clinical trials, at various phases, are in progress for effective medication against cancer. Most of them are immunotherapeutic, while a few are targeted to restore the aberrant genetic mutation. Preliminary studies at the murine level have been performed to target the restoration of the tumor suppressor gene mutation by Feldser *et al* [13]. This opens up a new possibility in not only inhibition of tumorigenesis, but also tumor regression.

The focus of this review is to discuss modern approaches for treatment of different forms of cancer that are aimed at tumor inhibition and regression. Therapeutic approaches mostly intended to (a) target biomarkers resulting from the altered cell signaling in cancer, (b) abnormal cytokine signaling (c) and most importantly, genetic manipulation with an aim to revert the process of oncogene formation or restore the impaired tumor suppressor activity; are the prime areas of interest. Success in the above areas could be a giant leap for mankind in conquering the menace of this incurable disease.

The Development of Cancer

A. All organs are not equally prone to cancer

Oncologists have recognized that the cancer rates vary from organ to organ in the body, and the variation of incidence is not attributed to the number of cells they contain. The investigations of the mechanism of carcinogenesis in cancer prone organs have pointed towards the presence of specific cell types vulnerable to neoplastic transformation, mainly due to attack by mutagens. For example, the lungs are cancer prone as the alveolar cells are exposed to airborne carcinogens like smoke, tetraethyl lead and radon [14, 15]; the colon cells susceptible to mutation by polycyclic hydrocarbons [16]; cervical uteri cells to sexually transmitted Human Papillomavirus (HPV) [17]. These correlative observations do not explain any overall pattern of organ-specific cancer incidence, but suggests that an inherent instability of evolved differentiation states [18]. In small intestine, the adult stem cells are continuously maintaining function by replacing old cells with new ones, making them a prone target for mutation. An interesting study using various tissue stem cells to determine why some organs generate cancer spontaneously was reported recently [19]. From different reports, almost all the organs of the body, including those mentioned before, are reported to be afflicted by cancer in varying rates of incidence.

In lung cancer, the carcinomas are derived from the alveolar epithelial cells, and peripheral lung tissue [20], that undergoes uncontrolled cell division evading apoptosis. A similar unrestricted growth also occurs in hepatocytes leading to hepatocarcinoma (liver cancer), and in associated cells in case of skin, colorectal and breast cancers. Contrastingly, though the adult neurons do not divide, brain cancers and associated neurocytoma of the central nervous system (CNS) arise due to the mitotic dysregulation of neural stem cells of the ventricular forebrain [21, 22]. Since they remain mitotic throughout life [23], they are prone to mutations and developing CNS tumors [24]. It is observed that most of the organs are prone to oncogenesis, except the heart, where primary cancers are rare except some benign tumors [25]. This is due to the fact that adult cardiac muscle cells (cardiomyocytes) do not divide when exposed to growth factors and the increase in size is attributed to hypertrophy [26].

B. Cancer: Details of the causes and conventional treatment

Carcinogenesis is caused by a multistep pathway resulting from sequential accumulation of mutations that occur in two classes of genes (a) Proto-oncogenes (normal genes coding for proteins that help in cell growth, differentiation and apoptosis) converted to oncogenes (mutated genes producing oncoproteins responsible for loss of regulation, increase in enzyme activity) [27] and (b) Tumor suppressor genes that encode proteins which regulate cell cycle and induce apoptosis of cells with chromosomal aberration [28]. These mutations disturb the fine homeostasis between the tumor formation and tumor suppression (Figure 1). Not only mutations, cancers arise also due to increase or decrease in a specific gene copy number, and translocations, resulting in dysregulated cell cycle and cell division. The uncontrolled cell division gives rise to tumors. Tumors could be benign, or malignant (potency to invade other tissues via the lymphatic system, and developing new blood vessels by a process called angiogenesis [29]). Cancer could also be caused by pathogenic infections [30]. Virus infections comprise most of the infection-related cancers, like Epstein-Barr virus (EBV) for B cell lymphoproliferative disease, Human Papillomavirus (HPV) for cervical cancer, Hepatitis B and C viruses (HBV and HCV) for hepatocarcinoma, Kaposi's sarcoma herpes virus for Kaposi's sarcoma and Human T cell leukemia virus (T cell leukemias). Bacterial infection may also increase the risk of cancer, as seen in *Helicobacter pylori*-induced gastric carcinoma [30].

A detailed and comparative table of the major life-threatening cancers is provided (Table 1). This fact-sheet describes the oncogenes responsible, the cell signaling pathways involved in carcinogenesis, the tumor suppressor gene inhibited in the process, the conventional treatment measures taken for management of the cancer and the corresponding references.

Modern Approaches to Cancer Therapy

Cancer treatment is mostly performed by the conventional methods; surgery to remove the localized tumor, chemotherapy and radiotherapy to destroy the neoplastic cells by the application of toxic chemicals or radiation, activation or suppressive immunotherapy to inhibit the progression of carcinogenic cell signaling, or hormone treatment. The choice of therapy depends on the stage of cancer, and also on the general health of the patient.

Cancer treatment can be approached as:

1. Therapy (after diagnosis of cancer)

1.1. Conventional

Table 1: The list of different types of cancers, their associated oncogene, risk, affected cell-signaling, tumor-suppressor gene, current treatment and references.

Cancer	Oncogene	Risk	Cell signaling affected	Tumor suppressor mutated	Current treatment	Ref.
Lung	K-ras	Smoke Asbestos Radon Inherited genes	Epidermal growth factor receptor (EGFR) ELK	p53 (17p) PTEN	Surgery Radiotherapy Targeted therapy Chemotherapy Palliative care	[31-36]
Liver		HBV HCV Aflatoxin	Self-antibodies attack mutated hepatocytes		Liver transplantation Surgical resection Sorafenib Percutaneous ethanol injection (PEI) Radiofrequency ablation (RFA) Selective Internal radiation therapy (SIRT) Cryosurgery Interventinal radiology	[37-43]
Breast	ras	Age Estrogen Radiation No breastfeeding	PI3K-Akt pathway HER-2/neu pathway (17 q) RAS/MEK/ERK pathway Leptin overexpression	PTEN BRCA1 BRCA 2	Hormone blocking therapy Chemotherapy Monoclonal antibodies Radiation Surgery	[44-51]
Colorectal	apc K-ras raf, c-Myc		Wnt ~β catenin signaling TGF~β- SMAD pathway Cox-2 overexpression MYC overexpression	p53 (17p) BAX	Surgery Chemotherapy Radiation Palliative care	[52-57]
Prostrate	c-Myc H-ras v-src	Age Family history HPV-16, 18 HSV-2	PI3K-Akt pathway TGF~β- SMAD pathway MIP-1 RUNX-2 expression	BRCA 1 BRCA 2 HPC 1 PTEN	Surgery Prostrate brachytherapy HIFU Chemotherapy Cryosurgery Hormonal therapy	[58-63]
Bladder	H-ras K-ras 2 rb-1 fgfr-3	Benzidine 2-napthylamine *Schistosoma haemotobium*	Wnt signaling P13K-Akt-mTOR EGFR signaling	KiSS-1	Transurethral resection (TUR)	[64-67]
Skin	p63 BRAF	UV radiation Cyclosporin A	TNFR-1 signaling Notch signaling	p53 CDKN- 2A	Thermo-chemotherapy Surgical excision	[68-72]

Table 1 Continues..

		HPV Inherited genes	Hedgehog signaling	CDK-4	radiation therapy Topical chemotherapy	
Renal	H-ras	Inherited genes Smoking	VHL-HIF pathway	VHL FH FLCN	Nephrectomy Cryotherapy Biological therapy Immunotherapy Arterial embolism	[73-75]
Uterine	K-ras c-erbB-2 c-Myc	Estrogen Family history radiation therapy to pelvis tamoxifen Age	PI3K-Akt pathway Ras-Raf-ERK pathway	Epithelial MIG-6 p53	Chemotherapy Hormone therapy Radiation therapy Abdominal hysterectomy	[76-80]
Pancreatic	K-ras SMAD4	family history age smoking Gingivitis *H.pylori*	Receptor Tyrosine Kinase signaling TGF-β signaling PI3K-PDK1 signaling	p53 CDKN-2A	Surgery Radiation Chemotherapy Radiofrequency Ablation Cryoablation	[81-85]
Bone	C-Myc N-myc C-fos	Radiation Bone marrow transplantation Inherited genes	TGF-β /SMAD signaling Ca2+ signaling HIF-1 IGF-1	p53 RB	Chemotherapy Radiotherapy Medication Amputation	[86-89]
Brain	c-erbB ros-1 c-myc gli	Vinyl Chloride Ionizing radiation	Akt pathway Notch signaling	p53	Surgery Radiotherapy Chemotherapy Shunt	[90-97]
Testicular	K-ras N-ras	cryptorchidism Family history Young age mumps	PGD2- SOX 9 pathway P13K-Akt pathway Wnt -β catenin signaling	p53 CDKN- 2A RB-1	Orchiectomy RPLND (retroperitoneal lymph node dissection) Chemotherapy Radiation therapy	[98-101]
Cervical	HCCR	HPV infection smoking HIV	Notch signaling Wnt -β catenin signaling Fibronectin-integrin signaling	p53 Cystatin E/M RASSF 1A	Hysterectomy Cone biopsy Trachelectomy Radiation therapy Combination Chemotherapy	[102-109]
Esophageal	PTK 7 HCCR-1	Obesity heredity Smoking and alcohol HPV Nitrosamines Coeliac disease hot drinks	EGFR signaling TLR-4 signaling NF-kB signaling	p53	Stent Esophagectomy PDT Radiotherapy Chemotherapy	[110-114]

- **1.1.1. Chemotherapy**
- **1.1.2. Radiotherapy**
- **1.1.3. Surgery**
- **1.1.4. Palliative care**
- **1.1.5. Angiogenesis inhibitors**
- **1.1.6. Hormone therapy**
- **1.1.7. Organ transplantation**

1.2. Modern (currently under research or trial)

- **1.2.1. Immunotherapy**
  - **1.2.1.1. Targeted therapy**
  - **1.2.1.2. Combined chemotherapy and immunotherapy**
  - **1.2.1.3. Therapeutic Vaccines**
- **1.2.2. Oncolytic virus**
- **1.2.3. Genetic manipulation**

2. Prevention (before diagnosis of cancer)

- **2.1. Screening for cancer biomarkers**
- **2.2. Detoxification**
- **2.3. Prophylactic vaccines**

The goal of treatment is the removal of cancer entirely without destroying the healthy cells. This could be achieved either by further inhibiting the process of tumorigenesis; or to revert the mutation process by un-mutating the tumor suppressor gene, or the oncogene back to proto-oncogene. Extensive scientific research has been ongoing to find new methods of treatment. A detailed discussion of the above sections and subsections would be devoted to the novel approaches and recent researches in the management of cancer.

1. Therapy (After Diagnosis of Cancer)

1.1. Conventional

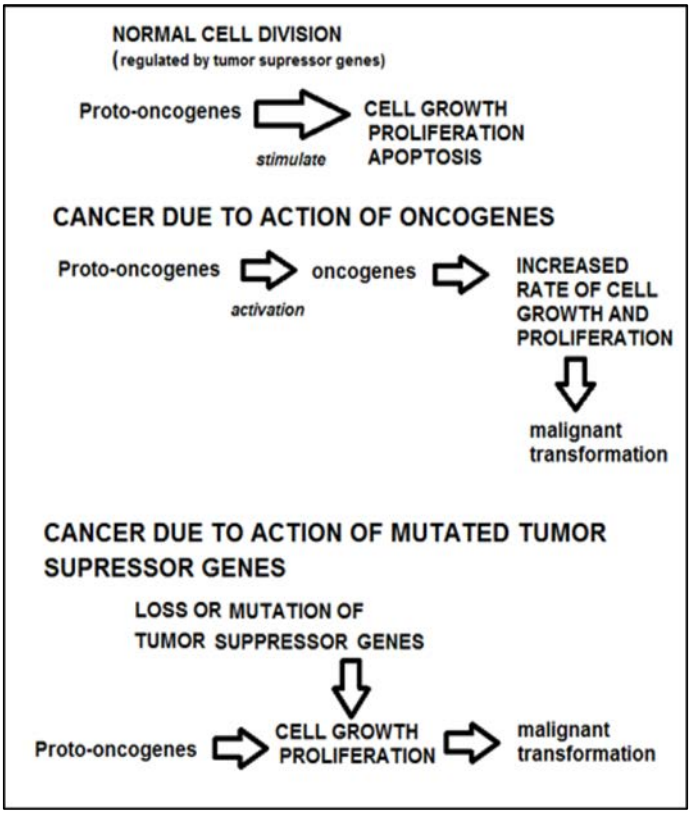
A list of the conventional and current cancer treatment methods have been provided in table 1 [31-114]. Unfortunately, the conventional methods like radiotherapy and chemotherapy have a negative effect on the normal cells as well [115]. Surgical methods are not able to control metastatic cancer. Angiogenesis inhibitors like Bevacizumab have been used to cut off tumor vasculature [116], but this drug cannot target all the factors utilized by the tumor for angiogenesis. Hormone therapy deals with the administration of certain hormones or inhibition of hormone receptors to control the process of a specific cancer, but they might have a stimulatory effect on another type of cancer. Some newer variations of the conventional treatment procedures have been developed, like the Stereotactic body radiation therapy (SBRT) which administers targeted radiation to a tumor while minimizing radiation to the surrounding normal tissue. This technique is utilized successfully for intracranial, base of skull tumors, but is also applicable to non-liver, non-lung oligometastatic diseases [117]. However, they are limited to the superficial and localized treatment, or suppression of the symptoms and improving the quality of life for the patient.

1.2. Modern (currently under research or trial)

1.2.1. Immunotherapy: This method of treatment induces, stimulates or suppresses the host immune response against the tumor cells within the body. Immunotherapies designed to enhance or stimulate the immune response is called *Enhancement Immunotherapy* while that designed to reduce or suppress the immune response is called *Suppression Immunotherapy*. The active agents that are used as a tool for immunotherapy are called *immunomodulators*, like cytokines, chemokines, synthetic CpG DNA or glucans [118].

1.2.1.1. Targeted therapy: Targeted therapy against cancer is now a very active research area. These drugs selectively target tumor-specific abnormal cellular processes. They accomplish their anti-carcinogenic activity by 3 processes; (1) activating human immune system directly against tumor cells, (2) inhibiting cellular proliferation, (3) inducing tumor anti-angiogenesis [119]. Prominent examples are the tyrosine kinase inhibitors imatinib and gefitinib. Drugs targeting the epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase, and vascular endothelial growth factor (VEGF) are now U.S. Food and Drug Administration approved for the treatment of advanced non-small cell lung cancer [120], as well as bladder cancer [121]. Programmed death 1 (PD-1) protein, a T-cell coinhibitory receptor, and one of its ligands, PD-L1, play a pivotal role in the ability of tumor cells to evade the host's immune system. Blockade of interactions between PD-1 and PD-L1 enhances immune function in vitro and mediates antitumor activity in preclinical models, as reported by Brahmer

Figure 1: The process of the evolution of cancer: (a) Conversion of proto-oncogene to oncogene (b) Dysregulation of the balance between tumor suppression and formation



JR et al [122].

Erlotinib inhibits the activation of epidermal growth factor receptor, mitogen activated protein kinase (MAPK), Akt and STAT3 [123, 124]. In the past couple of years (2011-2012) three drugs, Ipilimumab, (Human CTLA-4 monoclonal antibody, developed by Bristol Myers Squibb), Vemurafenib (inhibitor of the BRAF oncogene) and Vismodegib (inhibitor of the Hedgehog signaling) have been approved for metastatic melanomas and squamous cell carcinomas [125-127]. The drug, Vismodegib, is also undergoing clinical trials for a wide range of other malignancies, such as metastatic colorectal cancer, small cell lung cancer, advanced stomach cancer, and pancreatic cancer [128]. Currently, Regeneron Pharmaceuticals are also carrying out phase I clinical trials with anti ERBB 3 antibody (REGN1400) (US patent no. 4241391), Nesvacumab (Angiopoietin -2 monoclonal antibody, a novel angiogenesis target) are under phase I trials to control advanced stage malignancies [129]. Regeneron also produced ZALTRAP (VEGF binding protein), which is now FDA approved (in combination with other drugs) for advanced metastatic colorectal cancer treatment [130]. Blinatumomab, a bispecific antibody construct with potency to aggregate cytotoxic T cells, led to clearance of tumor cells from bone marrow and liver in non-Hodgkin lymphoma patients [131].

1.2.1.2. Combined chemotherapy and immunotherapy: A number of studies involving combination of chemotherapy and immunotherapy, though still at the pre-clinical/exploratory level, are showing great promise. The safety and activity of anti-CTLA-4 Ab alone or with a single dose of docetaxel in Human Refractory Prostate Cancer (HRPC) was evaluated by Small et al. against prostate cancer [132]. Myeloid derived suppressor cells (MDSC), T regulatory (Treg) cells are cell subsets that provide an immunosuppressive favorable environment for the tumor to grow. Hence they are potent targets whose suppression would lead to anti-tumor activities by NK cells and cytotoxic T cells [133-136]. Tecemotide (L-BLP25), a therapeutic vaccine developed by Oncothyreon, incorporates a 25-amino acid peptide sequence from the tumor-associated antigen MUC-1 in a liposomal formulation. The vaccine works by stimulating a T-cell mediated immune response to cancer cells expressing the target MUC-1, which is found in non-small cell lung, breast, colon, kidney, ovarian, pancreatic and prostate cancers [137, 138].

1.2.1.3. Therapeutic Vaccines: Cancer vaccines devised are of two types: Universal and specific. Specific vaccines are designed to treat specific types of cancers, while the universal vaccine is meant to fight cancer cells regardless of cancer type. In these two categories, there are more specific types of cancer vaccines. Each type of cancer vaccine works on the same basic idea: the vaccine, which contains tumor cells or antigens, stimulates the patient's immune system. It produces antibodies against the mutated cells and prevents relapses of the cancer. Here is a list of five kinds of cancer vaccines being developed:

• Antigen vaccines use tumor-specific antigens to stimulate the immune system. Upon administration of this vaccine into the cancerous lesion, or tumor, the immune system will produce antibodies, more specifically, cytotoxic T cells to attack the cancer cells carrying the specific antigen [139].

• Anti-idiotype vaccines act as antigens, triggering an immune response, producing anti-idiotype antibodies to attack the idiotypes [140].

• **Dendritic cell vaccines:** Patient's dendritic cells are extracted and stimulants are used to generate more dendritic cells. These dendritic cells are then cultured with antigens from the patient's cancer cells. This combination culture of dendritic cells is injected into the patient, and the dendritic cells work to program the T cells [141].

• **DNA vaccines:** Delivery of antigens by injection of the encoding DNA allows access to multiple antigen-presenting pathways. DNA construct is modified to induce selected effector functions. To activate immunity against tumor antigens, the tumor-derived sequences were fused to genes encoding microbial proteins. Epitope-specific DNA vaccination leads to powerful antitumor attack and can activate immunity from a profoundly tolerated repertoire. A wide range of cancers can be targeted [142].

• **Tumor cell vaccines:** Tumor cell vaccines can be produced by killing tumor cells from a patient and injecting them into him, who responds by producing antibodies. A study by Teshima et al (2001) reported that GM-CSF based tumor vaccines administered after allogenic T cell depleted bone marrow transplantation, potent anti-tumor activity without graft-vs-host reaction evoked after transplantation [143].

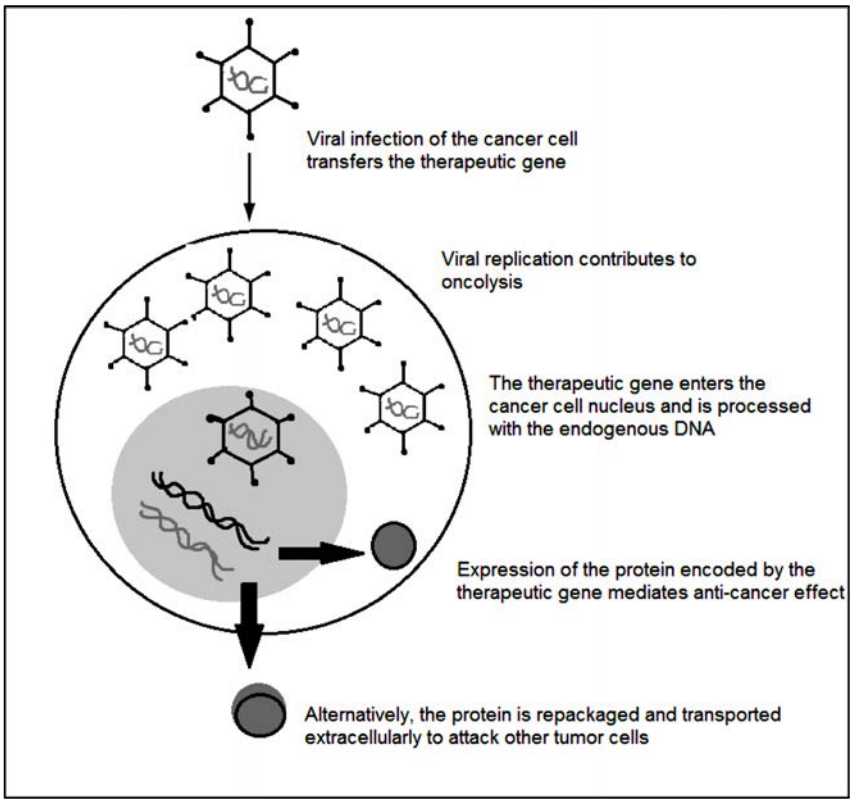
1.2.2. Oncolytic virus

An oncolytic virus is a virus that preferentially infects and kills cancer cells, and stimulates host anti-tumor immunity as well [144-146]. Only limited human trials had been performed as of 2011 [147]. Herpes simplex virus type 1 (HSV-1) mutant cannot replicate within differentiated or non-dividing cells but can do so in uncontrollably dividing cells, making it an attractive tool for tumor-targeting [148]. HSV1716 variants can be used to deliver genes to split a harmless prodrug inside cancer cells to release toxic chemotherapy [149], for the treatment of melanoma and squamous cell carcinoma of the head and neck [150, 151]. Other oncolytic viruses based on HSV are in clinical trials (OncoVex-GM-CSF), by Amgen, which has successfully completed a pivotal Phase III trial for advanced melanoma in 2013. A genetically modified adenovirus named H101 (Oncorine, developed by Shanghai Sunway Biotech) gained regulatory approval in 2005 from for the treatment of head and neck cancer [152]. This virus has been engineered to remove a viral defense mechanism that interacts with a normal human gene p53, which is very frequently dysregulated in cancer cells [152]. The mechanism of action of an oncolytic virus is shown in Figure 2.

1.2.3. Gene Therapy

Gene therapy is the medicine of the future cancer cure, because cancer is caused by genetic mutations, translocations and increased copy numbers of certain exons as well as defective tumor suppressor genes. At the MD Anderson Cancer center, scientists have identified mutated multiple advanced cancers gene (MMAC1) involved in some common cancers. Attempts

Figure 2: The mode of action of an oncolytic virus [35]



have been made to restore the mutated p53 gene to its normal form. Feldser et al [13], from MIT were among the first to report stage-specific sensitivity to p53 restoration during lung cancer progression in mice. Current gene therapies are at their infancy stage, tested pre-clinically only on animals. The gene therapy research refers to the replacement of a mutated gene with a functional gene delivered to target cells with a "vector." [153].

As a solution to the cancer cells immunosuppressive nature of the cancer cells, Kershaw et al [154] reported that T cells isolated from the blood of cancer patients be modified with genes encoding receptors that recognize cancer-specific antigens. This method could facilitate the penetration of engineered T cells into tumors expressing specific antigens [154, 155].

Neurosurgeons from the University of California, San Diego (UCSD) have conducted the first real-time MRI-guided gene therapy for patients with brain cancer, advancing the clinical trial of new cancer drug, Toca 511(vocimagene amiretrorepvec), which could be directly injected into a brain tumor. Toca 511 acts as like a retrovirus and selectively replicates in cancer cells, such as glioblastomas (brain tumors). Toca 511 creates an enzyme that changes an anti-fungal drug called fluorocytosine (5-FC), into an anti-cancer drug called 5-fluorouracil (5-FU). Following this injection, patients are given an oral formulation of 5-FC called Toca FC. When Toca FC comes into contact with cells infected with Toca 511, the cancer cells begin to die out [156].

Another novel and interesting approach in gene therapy is targeting the DNA methylation induced silencing of the tumor suppressor gene in case of breast cancer. It was observed that miRNA-29b, due to its complementarity to the 3' untranslated region of DNA methyltransferase 3A and 3B, could restore normal DNA methylation in MCF-7 breast cancer cell line, thereby inhibiting cell proliferation, DNA methyltransferase mRNA and the mutated TP73 tumor suppressor genes [157].

2. Prevention (Before Diagnosis of Cancer)

2.1. Screening for cancer biomarkers

Cancer screening aims to detect any transformation of cells before cancer appears, which might involve universal screening, or selectively screening people who are at risk with a certain cancer type [158, 159]. Though screening could lead to false-positive or false negative results, still it ensures early diagnosis and successful treatment. However, new genetic methods of cancer screening have been devised lately, like novel next generation sequencing (NGS) based approaches to sequence human DNA, and test for familial cancer syndromes (BRCA1, BRCA2 or TP53 [160] or detection of mutations to certain genes of therapeutic importance to cancer [161]. A method of ultrasensitive measurement of hotspot mutations in tumor DNA in blood have been reported by Narayan A et al, 2012 [162]. Besides, the BEAMing technique [163], allowed enumeration of mutant and wild-type sequences even when they were present in minute fractions and was sensitive enough to directly quantify the error rate of DNA polymerases used for PCR.

- *Breast cancer*: Screening mammography for all women aged 40 years and above every 2 years.
- *Cervical cancer:* The U.S. Preventive Services Task Force (USPSTF) strongly recommends cervical cancer screening in women who are sexually active at least until the age of 65, usually every three years [163].
- *Colorectal cancer:* Fecal occult blood testing, sigmoidoscopy, or colonoscopy, in adults, beginning at age 50 years have been recommended by USPSTF to screen for colorectal cancer. M2-PK Test is a new method of screening colorectal cancer [164] which is able to detect bleeding and non-bleeding colorectal cancers and polyps [165].
- *Prostate cancer:* The Prostate Specific Antigen (PSA) test for prostate cancer screening can effectively detect the antigen and subsequent diagnosis will lead to successful treatment [166].
- *Lung and other cancers:* There are insufficient evidences to recommend for or against lung, skin, bladder, testicular, ovarian or pancreatic cancer screening. However, as per the American Lung Association guideline for lung cancer screening, low-dose CT screening leads to 20% decrease in

cancer death and is recommended for current or previous smokers [167]. Recently, a groundbreaking invention of early pancreatic cancer screen by a 15 year old high school student of Maryland, Jack Andraka, has revolutionized detection and treatment of this disease. He developed a simple dip-stick test for levels of mesothelin, a biomarker for early stage pancreatic cancer found in blood and urine [168, 169] based on the research of Johnston FM et al 2009 [170].

- Candidate cancer biomarkers have been detected and research is ongoing to target them for development of screening against other cancers [171].

2.2. Detoxification

Vitamins and micronutrients obtained from natural sources of food prevent carcinogensis by inhibiting tumor initiation. D-glucaric acid and the enzyme beta-glucuronidase, found in fresh fruits and vegetables, have a role in early prevention of cancer [172].

2.3. Prophylactic vaccines

Placenta-derived heat shock protein gp96 induces prophylactic anti-tumor T cell responses against growth of transplantable melanoma or breast tumors in mice for 3 months. Placental gp96 activated HER2- and MUC1-specific T cell responses [173]. Mice vaccinated with embryonic stem cells (ESC) with GM-CSF, followed by implantable Lewis Lung carcinoma (LLC) challenge showed robust anti-tumor activity due to higher cytotoxic CD8+ T effector cell/CD4+CD25+FoxP3+ T reg cells along with decreased MDSC in the spleen [174]. In fact, a prophylactic vaccine developed by Merck & Co. is already present in the market against HPV-16 induced cervical cancer in young women, called Gardasil or Silgard [175, 176]. This cervical cancer vaccine was approved by FDA in 2008, and it is recommended to vaccinate young people before adolescence or potential sexual activity [177].

Summary

For decades, physicians and scientists have been actively searching for a permanent solution to cancer. Unlike other diseases, cancer is caused by genetic aberration, resulting in unregulated cell division and inhibition of programmed cell death (apoptosis). Such uncontrolled cell proliferation gives rise to tumors that can either remain *in situ* (benign) or invade other tissues by metastasis (malignant). Hence cancer is challenging to control with conventional methods of treatment like surgery, chemotherapy, radiotherapy, angiogenesis inhibitor drugs or others discussed above because they are not effective against metastatic cancers or not specifically toxic to cancer cells without destroying the normal cells. These superficial modes of treatment can only provide palliative care to prolong the life of the patient and relieve the symptoms for a certain period of time, but not cure it from the roots. This review covers ongoing researches that aim to target different forms of cancer at the genetic level to "un-mutate" the oncogene or tumor suppressor gene, or utilizing the body's own immune system against the tumor cells by administering targeted drugs and anaphylactic vaccines. Not only curative, but also preventive measures are being devised. Pre-diagnostic screenings for common cancers and prophylactic vaccines to prevent cancer are being developed. These studies are mostly at the pre-clinical or trial levels in renowned biopharmaceutical industries like Regeneron, Bristol Meyers Squibb, Bayer, Sanofi, and others. Some great products are already available in the market, like Gardasil as a preventive vaccine against HPV infection in young people. Using cancer biomarkers as a target to develop screening devices have gained tremendous interest. A recent report of a high school student Jack Andraka developing a dipstick based screening method of pancreatic cancer using the biomarker mesothelin from blood or urine has been a ground-breaking progress towards pancreatic cancer prevention [168-170].

This review has attempted to bring forward the latest changes in the conventional methods of cancer treatment, and more importantly, discuss the novel anti-cancer drugs developed at trial phases, or even pre-clinical/exploratory phases in laboratories and industries around the world. A special focus has been made on the discussion of gene therapy and immunotherapy procedures. These methods could be utilized to manipulate the genetic and immune machinery of the host with an aim to revert the process of oncogenesis, or destroy the tumor cells *in vivo*.

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