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Review

The significance of gene mutations across eight major cancer types

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ABSTRACT

Mutations occur spontaneously, which can be induced by either chemicals (*e.g.* benzene) or biological factors (*e.g.* virus). Not all mutations cause noticeable changes in cellular functions. However, mutation in key cellular genes leads to developmental disorders. It is one of the main ways in which proto-oncogenes can be changed into their oncogenic state. The progressive accumulation of multiple mutations throughout life leads to cancer. In the past few decades, extensive research on cancer biology has discovered many genes and pathways having role in cancer development. In this review, we tried to summarize the current knowledge of mutational effect on different cancer types and its consequences in brief for future reference and guidance of researchers in cancer biology.

1. Introduction

DNA is the prime hereditary material in most organisms except a few viruses. DNA in a cell can change as a consequence of environmental exposure to certain chemicals, ultraviolet radiation, other genetic factors, or even from defective DNA replication and repair process [1–3]. Hereditary alteration in the nucleotide sequence of an organism, viral genome or extra-chromosomal DNA is termed as mutation. It is the sudden change in the heritable characteristic which generates the variability that permits evolution to continue [4]. Without mutation, the gradual development of life from inorganic material would not have been possible. Mutations can occur at different scales ranging from small (single base) to large magnitude (multiple genes). Genetic alternations due to mutation, especially in the coding region of a gene shows drastic effect leading to various disease development and physical abnormalities [5]. Some mutations are beneficial for the organism, such as the development of immunoglobulin functional diversity. Mutations that are beneficial for the organism are selected by nature and such mutations accumulate within the gene pool [6]. Somatic mutations are genetic alteration that can be passed to the progeny of the mutated cell in the course of cell division within the life cycle of individual organism. Somatic mutations may lead to various diseases, including cancer. It differs from germ line mutations, which are inherited genetic alterations that occur in the germ cells. Somatic mutations are frequently caused by environmental factors, such as exposure to ultraviolet radiation or certain chemicals. For example, chemicals released in Bhopal gas tragedy in India are still affecting and inducing mutations in the genetic architecture of organisms living in that area [7]. Majority of the cancers about 90% are caused by somatic mutations and environmental factors while a few cancers are linked to germ line mutations.

The ultimate effect of germ line mutation is genetic variation; it is both the cause of genetic disease and the medium for evolution. Variation in the mutational process leads to different diseases, termed as mutational signatures. Except a few cancers which result from germline mutations such as the XP-related cancers, all other types of cancer are caused by somatic mutations, but the biological processes generating these mutations are limited [8]. The mutation catalogue from a cancer genome bears the footprints of mutational signatures [8]. Distinct combinations of mutation types in cancer genomes are generated by different mutational processes [9]. Somatic mutations occurring in cancer genomes may be the result of intrinsic DNA replication machinery, exogenous or endogenous mutation exposures, defective DNA repair, enzymatic modifications of DNA or some combinations of these [8]. In multiple mutational processes, mixtures of composite signatures are formed as these are based on “driver” mutations [10]. The joint effect of mutation-selection influences the observed frequency of mutation detected in an affected population. The strongly selected mutation will be found more frequently than weakly selected one in a condition where both the mutations are equally likely to occur. The effects of driver mutations lie on a continuum, including both mini-drivers and major-drivers. However, the relative selective advantages of individual driver mutations have not yet been quantified [11].

Immune system can suppress tumorigenesis, but also contribute to cancer initiation and progression suggesting a complex interaction between the immune system and cancer [12]. Recent insights on clinical

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studies and experimental mouse models of carcinogenesis, magnified our understandings about the intricate association between immune cells and developing tumors [13]. Tumor heterogeneity and metastasis play a substantial role in tumor growth [14]. The effect of epigenetic alternations in promoting the progression of cancer is now widely known. Two epigenetic processes *i.e.* DNA methylation and histone modification are well known for their role in cancer susceptibility. DNA methylation patterns is altered in cancer cells in comparison to normal cells. DNA hypomethylation leads to carcinogenesis *via* microsatellite instability, transcriptional activation and overexpression of oncogenes and loss of imprinting [15]. Thirty seven percent of somatic *p53* mutations occur at methyl CpGs, and these mutations are strongly implicated in the cause of cancer [16]. The abnormal histone acetylation leads to cancer development *via* its effect on many nuclear and cellular processes [17]. In addition to changes in histone acetylation, cancer cells are also distinguished by widespread changes in histone methylation patterns. Histone acetylation and DNA methylation are known to be intimately linked, as a number of proteins involved in DNA methylation (DNMTs and MBDs) directly interact with histone modifying enzymes (*histone methyltransferases* and *histone deacetylases*) [18]. Many studies have shown the effect of inflammation in tumorigenesis [19]. However, not all inflammatory diseases increase the risk of cancer and some of them may even reduce it. As a consequence of different forms of inflammation, the tumor microenvironment harbors different cell types which interact among themselves and decide the shape and the growth of tumour *i.e.* whether inflammation promotes tumor growth or anti-tumor immunity. Some forms of chronic inflammation are directly associated with the various environmental factors that lead to cancer and various risk factors. Cancer risk increases with the induction of inflammation by bacterial and viral infections [19,20]. Nearly 15% of the worldwide cancer incidence is associated with microbial infection [21]. Further evidence for the role of inflammation has come from the use of nonsteroidal anti-inflammatory drugs (NSAIDs) in the prevention of spontaneous tumor formation in people with familial adenomatous polyposis (FAP) [22]. Thus, cancer and inflammation are related by epidemiology, histopathology, inflammatory profiles, and the efficacy of anti-inflammatory drugs in prophylaxis [23].

The rates of different mutational processes vary among tumors and cancer types. In some types of cancer, somatic mutations are known to generate with exposures to UV radiation in the skin, tobacco consumption in lungs [8] or by abnormalities of maintenance of DNA *e.g.* defective DNA mismatch repair in some colorectal cancers [9]. Recently, Engstrom *et al,* 2017 confirmed that the mesenchymal-epithelial transition (MET) splice site mutations that result in the deletion of exon 14 (METex14del) are bona fide oncogenic drivers and sensitive to targeted therapeutics [24]. Tumor gene mutation status is becoming increasingly important in the treatment of patients with cancer. Below a few, distinct types of cancer-related to mutations are referred and reviewed on the basis of previous studies and its consequences are discussed in brief for future reference and guide.

2. Gene mutation related to different types of cancer

Lung cancer is cancer that starts in the lungs, characterized by multiple molecular/genetic changes over a long period of time [25,26]. Most common alterations are due to mutations of *Keap1*, members of the *ErbB* family, *KRAS, TP53*, *p16*, *BRAF, PIK3CA, AKT, FGFR2* and *MAP2K1* gene. Somatic mutation or homozygous mutation could alter *Keap1* activity that might lead to cancer by enhancing Nrf2 transcriptional activity [27]. Two mutations were observed in DGR domain of *Keap1 i.e.,* G430C in human lung cancer and G364C in lung adenocarcinoma [27]. *HER2* protein is a receptor tyrosine kinases of the *HER* family, found mostly in human cancers [28,29]. Mutations that occur in the kinase domain are in-frame insertions in exon 20, mostly involve the amino acid sequence Tyr-Val-Met-Ala [29]. *HER2* mutations are not present in tumors harboring *NRAS, BRAF, EGFR or KRAS2* mutations, the genes of which have also been implicated in the development of lung cancer [30]. About 30% of human lung adenocarcinoma is due to mutations in *KRAS* gene [31–34]. Pathogenesis of adenocarcinoma by *KRAS* involves the transformation of airway epithelial cell by activating the ERK-MAP kinase pathway [35,36]. Mutation of the *KRAS* gene also alters *EGFR* signaling pathways. *EGFR* plays an important role in the pathogenesis of adenocarcinoma of the lung rather than progression [37,38]. Mutation in *EGFR* leads to the activation of *EGFR* tyrosine kinase by destabilizing its auto inhibited conformation, which does not require ligand stimulation for maintenance [39]. Mutant *EGFR* scan transform fibroblasts and Ba/F3 cells [40,41]. Mutation in *EGFR* is more frequent in females and non-smokers [42,43]. *KRAS* and *EGFR* sequentially function in the MAPK signaling pathway, two molecules might be functionally redundant due to activating mutation which drivestumor growth [44–47]. *KRAS* mutations were never found in tumors with *EGFR* mutation and they show mutually exclusive relationship [37]. *EGFR* mutations are neither linked with the stage of diseases nor with age of the patients [37].

Point mutation results in recessive *p53* that is found in both cytoplasm and nucleus [48,49]. Mutated *p53* gene is metabolically stable and commonly associated with heat shock protein (hsp70) family [50]. Mutation disrupts a splice site in *TP53*, a characteristic feature of small cell lung cancer (SCLC) [38]. *TP53* mutations occur more frequently in smokers [51]. The *p16* is a tumor suppressor gene which is inactivated over 40% of NSCLCs [36]. *BRAF* mutations in NSCLC increase the kinase activity that leads to constitutive activation of MAPK2 and MAPK3 [52]. *AKT1* gene mutation in NSCLCs is about 1%. Mutation occurs in Glu17Lys, which encodes *protein kinase B*. This mutation alters the phosphoinositide-binding pocket, and activates *protein kinase B* [53]. *FGF*R1 somatic mutation is found in bronchoalveolar cancer [54]. *MAPKK1* (also known as *MEK*) is a Ser-Thr *kinase* that is linked with *B-RAF* at downstream and activates *MAPK2* and *MAPK3* [55]. *EGFR, KRAS, HER2, PIK3CA,* and *BRAF* mutations are mutually exclusive to *MAP2K1* mutations [29].

Breast cancer is the leading cancer type in women having a lifetime risk of more than 10%. Women with a *BRCA1* or *BRCA2* mutation have a cumulative lifetime risk of invasive breast cancer (up to the age of 70 years) of 55–85% and of invasive epithelial ovarian cancer of 15–65% [56,57]. It was estimated that the penetrance of *BRCA1* gene is 59% by age 50 years and 83% by age 70 years [58]. Studies indicated that women who carry germline *BRCA1* mutations and undergo bilateral prophylactic oophorectomy may experience a reduction in breast cancer [59–62]. The majority of the families with a clearly dominant predisposition to breast and ovarian cancer are now known to harbor germline mutations in either *BRCA1* or*BRCA2* genes [56,63,64]. Many distinct mutations in *BRCA2* are related to the risk of developing prostate cancer, laryngeal cancer, and pancreatic cancer [57,65,66]. Tumors with *BRCA1* mutations are generally negative for both estrogen and progesterone receptors whereas most tumors with the *BRCA2* mutation are positive for these hormone receptors [67–70]. Breast cancer has somatic mutation spectra dominated by C-to-T transition [30,71–78]. Most of these mutations occur at hydrolytically disfavored non-methylated cytokines throughout the genome and are sometimes clustered [77,79]. DNA cytosine deaminase APOBEC3B is a probable source of mutations [80]. APOBEC3B messenger RNA is upregulated in most primary breast cancer tumors and breast cancer cell lines. Tumors that express a high level of APOBEC3B have twice as many mutations as those that express at low levels and more likely to have a mutation in *TP53* gene [80].

In breast cancer, *PIK3CA* gene is frequently mutated at exon 9 and 20 [81]. The phosphatase and tensin homolog gene (*PTEN)* is mutated in breast cancer [82]. *PALB2* is a new addition to the growing list of genes associated with approx 2-fold increased risk of breast cancer [83]. *CHEK2* mutations are also associated with increased risk of breast cancer [84]. A rare mutation of *BRIP1* was also identified in breast cancer families [85]. *RAD50* conferred an approx 4 fold increase in the

risk of breast cancer [86]. Women with mutations in the *p53* gene may be at increased risk of developing breast cancer. However, mutations of the *p53* gene are rare, affecting an estimated 1 in 10,000 individuals [87]. Mutations in *HRAS1*, the Cowden disease gene, *p65,* and *TSG101* may also confer a higher risk of developing breast cancer [87]. Breast cancer is uncommon in male accounting for only about 1% of all breast cancers and 1% of all malignancies detected in man [88].

Oral cancer is defined as the cancer formed in the tissues of the oral cavity or the oropharynx. It belongs to a larger group of cancers called head and neck cancers. According to GloboCan 2018, it is the 7th most common cancer preceded by breast, lung, colorectal, prostate, stomach, and liver cancer. Oral cancer is high in case of men in India [89]. Smoking, alcohol misuse, regular use of betel-quid and infection by human papillomavirus increase the risk of oral cancer [90]. Betel-quid chewing with or without areca nut (*Areca catechu*) and tobacco, is traditionally popular in India and is known to cause oral cancer [91,92]. The chewing of betel-quid with or without tobacco helps in the formation of nitrosamine, a carcinogen [92,93].

According to Oral Cancer Gene Database (Version II), 374 genes are known to involve in oral cancer [94]. More than 63 karyotypes have been described in oral cancer and the recurrent loss of chromosome 9, 13, 18 and Y has been reported [95]. In most of the head and neck cancer cells, a deleted region in chromosome 9p2122 is observed [96,97]. Frequently deleted regions in 3p and 13q may also yield new tumor-suppressing genes (*TSGs*) or oral carcinogenesis [98]. Aberrant expression of *EGPR* and *TGF*-alpha leads to malignancy in human oral cancer [99,100]. Combined expression of *TGF*-alpha and *EGPR* formed more aggressive tumors than those formed by *EGPR* alone [101]. *TSGs* or *anti-oncogenes* possess negative regulatory controls which are lost due to chromosomal aberrations during tumor formation. Functional loss of multiple *TSGs* or anti-oncogenes is due to chromosomal aberrations during tumor formation, a major event in the development of malignancies [102,103]. Polymerase chain reaction has revealed a high frequency of *p53* mutations in patients with squamous-cell carcinoma associated with a history of tobacco and alcohol [104].

Cell surface molecules play important roles in inhibiting oral keratinocyte proliferation [105]. E-cadherin and DOC are found to be down-regulated during oral cancer development [106]. Adenomatous polyposis coli (*APC*) gene, that produces G-like protein, is frequently mutated in certain familial colorectal cancers [107]. Further studies disclose that the *APC* gene may be altered in the premalignant oral lesions [108]. *RAR-b, retinoic acid receptor-beta* is seen to be down-regulated in the head and neck cancer [109]. The frequent deletions among betel quid and/or tobacco chewers are seen in chromosome arms 3p (genes *FHIT* and *RARB*), 4q, 5q, 9q and 18q [110–112]. The mRNA production of *cyclooxygenase-2* (*COX-2*) gene is upregulated which results in inflammatory response [113]. In Gingivo-buccal oral squamous cell carcinoma (OSCC-GB),*USP9X, MLL4, ARID2, UNC13C* and *TRPM3* genes were found to be frequently altered [114].

In the recent few years, thyroid cancer has emerged as a common endocrine malignancy and has been rapidly increasing its global incidence [115,116]. Thyroid cancer has many histological types and subtypes, based on different cellular origins, characteristics, and prognoses [117]. Majority of the thyroid malignancies occur in the follicular thyroid cells, while a small proportion of thyroid malignancies occur in the parafollicular C cells. Malignancies occurring in the parafollicular C cells are called medullary thyroid cancer (MTC), occur as a result of aberrant activation of RET signaling caused by RET mutations. The papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC) are collectively classified as differentiated thyroid cancer (DTC) [118].

Point mutations of the *BRAF* gene at codon number 600 is found in approximately 45% of PTC [119]. Point mutations at codon 12, 13 and 61 in the three *RAS* genes (*HRAS, KRAS*, and *NRAS*) have been found in pediatric papillary thyroid carcinoma [120–122]. *NRAS* codon 61 and *HRAS* codon 61 mutations are most common in thyroid cancer [122]. Proteins encoded by the *RAS* gene are the components of multiple intracellular signaling cascades such as MAP-Kinase pathway and PI3K-AKT pathway [123]. Mutations in the *RAS*gene cause the loss of its GTPase activity, thereby locking *RAS* in an active state. *RAS* mutations activate the PI3K-AKT pathway in thyroid tumorigenesis, which has been suggested by the preferential association of *RAS* mutations with AKT phosphorylation in thyroid cancer [124–127]. Chromosomal rearrangements of the RET/PTC have been found in most PTC [128]. Most common chromosomal rearrangement includes RET/PTC1 and RET/PTC3, in which the *RET* gene fuses either to CCDC6 (H4) or NCOA4 (ELE1 or RFG), respectively [129,130]. As all the fusion partners of RET residues occur in the long arm of chromosome 10, the rearrangements are paracentric and intrachromosomal inversions [131,132]. RET/PTC2 and nine more rearrangements have been discovered recently which are formed by RET fusion with genes located on different chromosomes [120,121,133–139]. Rearrangements also lead to the fusion of a portion of the *PAX8* gene and the *PPAR*γ gene results in the overexpression of the chimeric PAX8/PPARγ protein [135,140]. This type of rearrangement is a prototypic alteration which has been found in 30–35% of follicular thyroid cancers [139,141,142]. In Hurthle-cell thyroid carcinoma (HCTC), mutations occur in *NADP dehydrogenase* (ubiquinone) 1α sub-complex 13 (NDUFA13) also known as GRIM19 [143]. This type of carcinoma does not harbor*BRAF, RAS* or *RET-PTC* mutations [144,145]. Mutations in *β-catenin (CTNNβ1),p53*, *isocitrate dehydrogenase 1* (*IDH1*), *anaplastic lymphoma-kinase* (*ALK*) and *epidermal growth factor receptor* (*EGFR*) have been found to occur in thyroid carcinoma [146–153].

Gastric cancer is one of the most common malignant diseases having the highest mortality rates worldwide and adenocarcinoma is associated with 95% of gastric cancer cases [154]. On the basis of Lauren's classification, gastric cancers are divided into two main subtypes-intestinal and diffuse [155]. Less than 3% of the gastric cancer cases are linked to hereditary cancer syndrome. Diffuse Gastric Cancer (HDGC) is the most frequent hereditary gastric cancer that occurs due to the germ line mutation in *CDH1* genes [156–158]. Hereditary nonpolyposis colon cancer patients haveahigh risk of intestinal gastric cancer which arises through disordered DNA repair mechanism as a result of mutation in*MSH2* and *MSH1* genes [155]. In precancerous lesions, *p16* methylation is associated with *H. pylori* infection in the intermediate metaplasia stage [155]. The risk of gastric cancer can be detected by the genomic instability in the intestinal metaplasia and can also be used for the clinical evaluation of malignant potential [159].

Almost 50% of the gastric cancer is due to microsatellite instability [155]. It is the result of the epigenetic changes of the mismatch repair genes especially *MSH1* gene [160–162]. Impairment of the DNA mismatch repair genes due to hypermethylation in the promoter region is the most common epigenetic change which leads to multiple mutations with simple nucleotide repeats and the expression levels of many downstream genes. They affect and exert functional consequences on a number of cell functions such as cell signaling, cell cycle and tumor suppression [163]. High level of microsatellite instability tumors has better survival rate as compared to the tumors having a low level of microsatellite instability [164]. Malignancy can be detected by the chromosomal instability and can occur as an early or late event in disease progression [155,165]. There are large numbers of chromosomal aberrations in gastric cancer; the gain of copy number associated with the intestinal gastric cancer involves 8q, 17q, and 20q whereas in the diffuse gastric cancer the copy number gain is associated with the 12q and 13q [166–173]. Breakpoint mutation in *SLCIA2* gene responsible for chromosomal inversion produces a SLCIA2-fusion protein which alters the growth properties of cells probably by causing abnormalities in the metabolic pathways [174]. *ROS1* gene is another novel fusion protein which is produced as a result of the genetic rearrangements in gastric cancer [175].

Skin cancer is currently the most common type of human cancer, and is of particular concern since its incidence is increasing at an alarming rate [176]. Skin cancer is mainly divided into melanoma and

non-melanoma skin cancers (NMSCs), the latter includes basal and squamous cell carcinomas (BCC and SCC), respectively [177]. The skin has *p53*-dependent cellular proofreading responses to DNA damage in which transformed cells undergo apoptosis [178]. Mutation in the *p53*tumor suppressor gene appears to be an early genetic event in the development of UV-induced skin cancer [179].The location of mutation in the *p53* gene is not random and hotspot of C to T and CC to TT mutations are found in skin [180–182]. In human, *p53* gene defects are involved in more than 50% of malignancies including melanoma and non-melanoma skin cancer [177]. *p53* gene inactivation may result fromapoint mutation, deletion, and insertional mutation [183]. In melanomas, *p53* gene mutations are late events that occur during progression to a higher grade of malignancy whereas it is an early event in non- melanomas skin cancer [184].

Most *RAS* mutations found in various types of human cancers occur in codons 12, 13 and 61 and result in the continuous activation of *RAS*-mediated signal transduction [185]. A number of studies have now shown that human skin cancers contain mutation in all three members, *HRAS, KRAS, NRAS*of the *RAS*family [186]. Human skin tumors originating on the sun exposed body sites revealed that 16–40 skin tumor casesanalysed (11 of 24 SCCs and 5 of 16 BCCs) contained the identical G →T mutation (glycine to valine) at codon 12 of the H-*RAS* oncogene [187]. The*p16*protein is expressed in both melanoma and non-melanoma skin cancer. In melanomas, *p16* protein expression shows a gradual down-regulation, where, in non-melanomaskin cancer*p16* protein expression shows a gradual up-regulation [188,189]. Nuclear factor erythroid-related factor 2 (Nrf2) also plays an important role in the pathogenesis of SCC [190]. Mutation in *XPF, XPD, ERCC1* genes result in an increased incidence of skin cancer in human [191].

Renal cell cancer (RCC) occurs in adults. In RCC changes in miRNA expression have been documented, although the patterns reported are not consistent [192–200]. Kidney cancer is frequently associated with the Von Hippel Lindau (VHL) tumor suppressor inactivation, resulting in elevated levels of hypoxia inducible transcription factors (HIF) [201]. Renal cancer comprises a number of distinct types of cancers that occur in kidney, each with a different response to therapy and different genes causing the defect [202,203]. Kidney cancer affects nearly 270,000 patients worldwide annually [204]. Genes playing acrucial role in kidney cancer are *VHL*, *MET*, *FLCN*, *TSC1*, *TSC2*, *FH* and *SDH* [205,206]. Kidney cancer may be in non-inheritedas well as hereditary (inherited) forms. Most of the genetic basis of kidney cancer is concerned with the hereditary forms of kidney cancer [206]. There are four types of hereditary kidney cancer: VHL, HPRC, BHD and HLRCC. Effective forms of therapy for this disease can be developed by understanding the genetic basis of kidney cancer [205].The renal tumors associated with VHL lead to clear cell renal carcinoma [207]. In nearly 100% of VHL families, germline mutation of the *VHL* gene is identified [208]. The gene *VHL* possesses the characteristics of a tumor suppressor gene and alteration of both copies of the gene is found in sporadic clear cell renal carcinoma and VHL- associated tumors [205].

Hereditary papillary renal carcinoma (HPRC) is a cancer syndrome, in which affected individuals are at risk of the development of multifocal, bilateral, type 1 papillary renal carcinoma [209,210]. In renal carcinoma, mutations are confined to exons which encode the tyrosine kinase domain. In affected individuals in HPRC kindreds, activating mutations in the tyrosine kinase domain was found [211]. In a subset of sporadic, type 1 papillary renal cell carcinoma *MET* mutations were also found [212].Around 22 mutations mainly frameshift or nonsense mutations were identified in BHD (Birt-Hogg-Dube syndrome) kindreds. BHD is a cancer syndrome in which individuals develop cutaneous fibrofolliculomas, pulmonary cysts and renal tumors [213,214]. HLRCC is a cancer syndrome in which individuals are at a risk of developing cutaneous and uterine leiomyomas and kidney cancer [215].

Pancreatic cancer is the fourth-leading cause of cancer death in the USA leading to an estimated death of ˜44,330 per year. Most of the cases of pancreatic cancer are sporadic although ˜10% of the overall cases are believed to be caused by inherited genetic factors [216–218]. It was observed that a family history of pancreatic cancer increases the risk of developing cancer by ˜3 folds [216,219–221]. The risks further increase to 9 folds when the individuals have a pancreatic cancer patient among a first-degree relative [222,223]. When the number of the first degree relative with pancreatic cancer rises above 2, the risk increases to 57 folds [216,224]. Till date, around 63 genetic alterations have been found to be linked with pancreatic cancer, of which a majority have been found to be point mutations [225]. *KRAS* gene has been found to be mutated in over 90% cases of pancreatic cancer [226,227].The wild-type *KRAS* gene encodes for glycine (GGT) at codon 12, and the most common amino acid substitution is aspartic acid for glycine (46%), followed by valine (32%), arginine (13%), cysteine (5%), serine (1%–2%), and alanine (< 1%) [228]. The *BRAF* gene is a downstream molecule in *RAS* signaling and a frequent candidate for mutation in various cancers including 60% of melanomas and 10% of the colorectal carcinomas [229–231]. This elucidation strengthens the mutual involvement of *KRAS2/BRAF* mutations in the onset of pancreatic ductal carcinogenesis. The frequency of cyclin E (proto-oncogene) overexpression in pancreatic cancer patients is nearly 6% [231].

The frequency of *p53* mutations in pancreatic cancer patients is lower as compared to mutations in the *KRAS* gene. Murphy et al.2002identified that 5 out of their 29 pancreatic cancer patients (17.2%) harbored a deleterious mutation of the *BRCA2* gene [216]. The biallelic inactivation of *BRCA2* is a relatively late event in the progression of pancreatic tumorigenesis [232]. Another study has linked a 2bp deletion (6819delTG) of *BRCA2* gene with high penetrance of pancreatic cancer [216]. Independent studies have established *PALB2* as the second most common mutational target associated with familial pancreatic cancer, the first being *BRCA2* [233]. Two mutational hotspots have been detected within the *MTS1* gene, codons 72 and 102 [234–237].The *MTS1* gene along with *p53* plays an important role in regulating the onset of pancreatic cancer [238]. Pancreatic cancer may also be identified by detecting the presence of a combination of *MTS1* and *KRAS* mutations in the primary tumor [238].

3. Application of mutational information and advances already made

Any decision on lung cancer therapy is based on histological considerations. The discovery of mutational effect on tumor progression in subsets of non-small-cell lung cancer (NSCLC) has transformed the clinical management of lung cancer. The identification of different biomarkers and treatments based on these biomarkers has improved the cancer treatment in recent years (Fig. 1). Targeting EGFR mutations or the *EML4-ALK* rearrangement with tyrosine kinase inhibitors has transformed the clinical management [239]. The most significant paradigm change in the last 10 years for NSCLC management was heralded by the use of *EGFR* TKIs as first-line therapy for patients with a targetable EGFR driver mutation [240]. Tyrosine kinase inhibitors (TKIs), Gefitinib (Iressa), and erlotinib (Tarceva) are used to treat non–small cell lung cancers (NSCLCs) that have activating mutations in *EFGR* gene which inhibits the epidermal growth factor receptor (EGFR) kinase [241]. The identification of novel oncogenic drivers in lung adenocarcinoma *i.e.* mutations in *BRAF*, *PIK3CA*, *HER2*, and fusions in *ROS1* and *RET* are currently being validated as therapeutic targets in clinical trials.Park et al., 2016 showed that afatinib significantly improve the outcomes in treatment-naive patients with EGFR-mutated NSCLC compared with gefitinib, with a manageable tolerability profile [242]. BEZ235, a small inhibitor molecule shows antitumor activity by targeting PI3K and mTOR proteins [243]. In ATR-deficient cells, the ATM-dependent DDR could serve as an important tumor-suppressive defense machinery *in vivo* [244]. Mutations in MAP2K1display sensitivity to the small-molecule non-ATP-competitive MAPKK1 inhibitor, AZD6244 [245]. EFGR TKI response rate is about 60%–80%. Patient

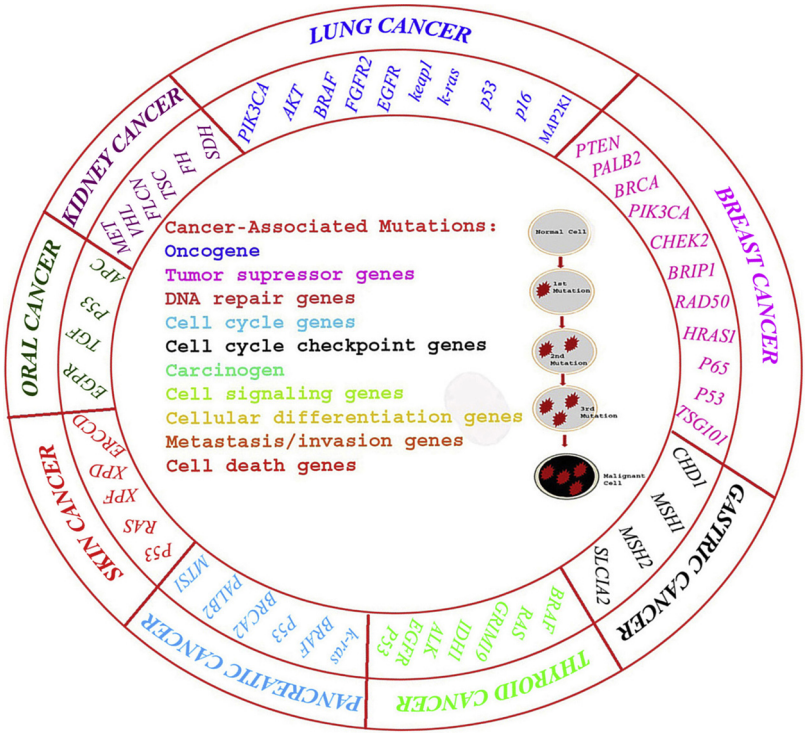

Fig. 1. This figure highlights the role of mutation and the genes that play a vital role in cancer development.

with ALK positive mutation responds to about 60% by the inhibitor crizotinib [246]. However, the efficacy of crizotinib in these cancers is limited by poor activity in the CNS and the frequent emergence of drug resistance in a relatively short time [247].

Genome-wide changes in histone acetylation can serve as molecular biomarker of tumor *versus* normal tissue [248]. Over-expression of histone deacetylases (HDACs) correlates with the decreases in both disease-free and overall survival in several cancer types, such as prostate, colorectal, breast, lung, liver, and gastric cancer [248]. Adjuvant systemic therapy substantially improves disease-free and overall survival in both pre-menopausal and post-menopausal women upto the age of 70 years with lymph node positive or negative breast cancer [249,250]. Anthracyclines as monotherapy or in combined drug regimen are considered as the most effective drugs in breast cancer [251]. Trastuzumab (Herceptin) a monoclonal antibody against the growth factor receptor HER2, has been shown to improve survival in HER2 over-expressing breast cancer patients, and as an adjuvant therapy in combination with other treatments [252,253]. Many potential inhibitors of matrix metalloproteinases (MMPs) were designed and assessed for anti-cancer properties. The key to the design of effective MPIs (metalloproteinase inhibitor) is understanding the roles and properties of individual MMPs. Originally MPI design was based on small peptides that mimicked MMP substrates [254]. MicroRNA-335 and miR-126 are also identified as metastasis suppressor miRNA in human breast cancer [255]. Robinson et al., 2013 put forwarded the idea that activating mutations in ESR1 are a key mechanism in acquired endocrine resistance in breast cancer therapy [256]. Strategies for the reduction of the risk of primary and contralateral breast cancer include prophylactic mastectomy and chemoprevention [257,258]. The use of olaparib (an oral poly ADP-ribose) in germline *BRCA1* and *BRCA2 (BRCA1/2)* –associated breast and ovarian cancers are in clinical trials [259]. In breast cancer, tamoxifen reduces the risk of primary invasive and premalignancy in women at high-risk and of contralateral breast cancer in unselected women [260]. Microarray analysis has been used to distinguish cancer associated with *BRCA1* or *BRCA2* mutation [261,262] to determine estrogen-receptor status [262–264] and lymph-node status [265,266].

Prevention and early detection of oral cancer remain the goals of national efforts to reduce the impact of this disease in public. Inhibition of EGFR plays an important role in tumor progression. Anti-EGFR antibodies namely 225 and cetuximab shows antitumor activity in several cancer cell lines, including oral cancer [267].To a significant degree, the oral problems associated with radiation therapy can be prevented or minimized through optimal management [268]. Surgical treatment is the mainstay of therapy for patients with oral cancer, particularly in advanced stages of cancer [269]. Radiotherapy and photodynamic and topical cytotoxic radiotherapy (RT), is used for treating oral intraepithelial neoplasia (IEN) [270]. Over the last decade, oral chemotherapy has generally failed to keep pace with increasing use of i.v.cytotoxics [270]. High-dose of the retinoid 13-cis-retinoic acid (13cRA) can reverse oral IEN and reduce the SPT risk of definitively treated head and neck cancer patients [270]. High dose of 13cRA is not acceptable for long-term prevention.

Radiotherapy and chemotherapy are the treatment options for the advanced stages of differentiated thyroid cancer (DTC) and medullary thyroid cancer (MTC) [271]. The treatment regimen for advanced cancer treatment includes bleomycin, doxorubicin, platinum-containing compounds or a combination of these agents. In the field of molecular mechanisms of thyroid cancer, recent research has underlined the role of oncogenic kinases [119]. This field now focuses on the efforts for the use of new targeted therapeutics, especially the ones that inhibit kinases involved in signaling, cellular growth and angiogenesis [272]. A wide variety of multi-targeted kinase inhibitors has entered clinical trials for patients with metastatic thyroid cancers since 2005 [273]. Most of these agents inhibit vascular endothelial growth factor receptor (VEGFR) and have a potent anti-angiogenetic role because of the similarity between RET and VEGFR kinases. The RET/RAS/RAF pathway is interconnected with the epidermal growth factor (EGF)-activated cascade and leads to the synthesis of vascular endothelial growth factor (VEGF) and VEGF receptor [271]. Mutations in the *BRAF* oncogene confer new or enhanced activity on a protein, which has been found to be the frequent genetic alterations in patients with papillary thyroid cancer. Drugs targeting this pathway could play a significant role in the treatment of this disease. Some of the therapeutic drugs

include sorafenib, which has an RAF-RET and VEGFR-inhibiting activity; axitinib having VEGFR, C-KIT and PDGFR inhibiting activity; pazopanib possessing VEGFR and PDGFR inhibiting activity; sunitinib inhibiting a multikinase inhibitor, E7080 and V*EGFR* [271]. Cobazotinib targets *MET*, V*EGFR*2 and RET whereas vandetanib targets RET, EGFR and VEGFR for the treatment of metastatic MTC [274]. However, numerous side effects of these multi-targeted kinase inhibitors have been reported in different trials with several patients requiring a dose reduction to improve tolerability. The commonly occurring side effects of these inhibitors involved the cardiovascular system such as hypertension, cardiomyopathy, stroke and skin rashes [273]. In some cases, TSH elevations were observed during motesanib therapy [275]. Some of the antineoplastic drugs have been found to be interacting *with FGFR3, WEE1, PSMD1, MERTK, RARG* and *ESR2* genes which are up-regulated and down-regulated in anaplastic thyroid cancer. Carfilzomib and bortezomib are the proteasome inhibitors which have been successfully used in inhibiting ATC (Anaplastic thyroid carcinoma)tumor growth *in vitro* and *in vivo* [276,277]. The *RARG* gene encodes the retinoic acid receptor gamma and treatment of ATC cell lines with retinoic acid has significantly elevated iodine uptake and altered expression of genes involved in cell growth and differentiation [278]. ATC is a highly aggressive tumor with a poor prognosis which is often diagnosed in the late stage with theregional and distant spread. Therefore, the demand for new targeted therapeutic molecule is highly essential for the treatment of ATC. *MTOR, MET, WEE1, PSMD1, MERTK, FGFR3, RARG* and *ESR2* pose as potential therapeutic targets which may lead to the introduction of novel therapies in ATC and these genes might function as targets for inhibitory drugs [279].

In gastric cancer, the protein encoded by the *HER2* oncogene is the first successfully exploited molecule in the therapies for gastric cancer [280]. Other therapeutics includes the mesenchymal epithelial transition (MET) pathway. MET is a tyrosine kinase receptor, several signalling transduction cascades become activated by the auto-phosphorylation of the MET leading to cancer cell proliferation, invasion and metastasis [281]. So the development of the MET inhibitors can be used for the therapeutic purpose. Rilotumumab is a monoclonal antibody used for targeting MET. Several other promising molecular targets includes VEGR2, FGFR1, 2, HER3, and members of the PI3K/AKT/mTOR pathway [282].

Phototherapy is currently being used to treat various epidermal diseases. These phototherapies are conducted by using broadband UVB (290–320 nm), and narrowband UVB (311–313 nm), UVA- 1 (340–400 nm), and proralens plus (PUVA). PUVA therapy is mutagenic and carcinogenic. The determinants of the risk of NMSC and melanomas in PUVA-treated patients can vary with the dose and length of time of exposure to PUVA. Patients with PUVA may also develop large, irregular, unevenly pigmented, dark lentigines known as PUVA lentigines, which may be a precursor of melanoma. PUVA is a major risk factor for many skin conditions and a useful tool for treating several skin conditions. Natural products having anti-skin cancer activity were discussed and reviewed by Chinembiri et al. [283].

For effective targeting of C-Met pathway three basic strategies are used, firstly antagonism of ligand/ receptor interaction, secondly inhibition of tyrosine kinase catalytic activity and lastly by blockade of receptor/ effectors interaction. Conventional and C-Met –targeted therapies when combined together may offer promise for specific cancers [284]. Agents like geldanamycin can attenuate the supply of new receptors to the cell surface with inhibitors of other receptor functions, lowering the dose of each, reducing the level of drug toxicity and the pressure for drug-resistant mutations. For patients with localized clear cell type1 papillary orchromophobe kidney cancer the conventional approach to therapy has been to surgically remove the tumor. The surgical approach of partial nephrectomy has been developed over the past two decades and is now a widely used approach for most patients with kidney cancers that are 7 cm or less in size. In clinical trials, the role of adjuvant therapy is performed in patients with metastatic disease [285]. TheVHL pathway leads to the development of therapeutic approaches for patients with clear cell kidney cancer [286,287]. Agents targeting the VHL pathway such as temsirolimus, everolimus, sunitinib, maleate, sorafenib, pazopanib and axitinib having significant anti-tumour activity in patients with clear cell kidney cancer have been identified by several studies [288].

Pancreatic cancer is associated with 12 signaling pathways constituting mutations in 63 genes [289]. Cytotoxic chemotherapy based approach using gemcitabine is the most widely used therapeutic technique that has been applied to tackle pancreatic ductal adenocarcinoma (PDAC). Molecular approaches have been used to target oncogenes and their downstream signaling molecules. The simultaneous inactivation of epidermal growth factor and MEK pathway which are downstream signaling components of the KRAS signal cascade using erlotinib and selumetinib respectively have shown some success in stabilizing the disease [290,291]. Poly(ADP-ribose) polymerase (PARP) inhibitor in combination with gemcitabine shows strong anti-tumour activity [291,292]. The targeted use of pegylated recombinant hyaluronidase against hyaluronan accompanied with gemcitabine have proven to be very efficient in preliminary mouse model studies [291,293]. Since cancer stem cells (CSCs) constitute a very small percentage of the cells in a pancreatic tumor; these cells have a 100-fold higher ability compared to the non-tumorigenic ones [294]. Moreover, the CSCs can resist chemotherapy and radiation to a greater extent than other cancer cells [295,296]. Pancreatic CSCs have been found to overexpress epithelial cell adhesion molecules (EpCAM). These features of the pancreatic CSCs have been used to design MT110, a bispecific antibody that is specific for both EpCAM on the CSCs as well as the T cell-CD3 complexes on the T cells. This immunotherapeutic technique causes the selective elimination of the pancreatic CSCs by the T cells [291,297]. Transfer of adoptive T cells and targeting of epigenetic regulators are some of the future prospects that are being worked upon [291]. Vaccine therapies against PDAC cells have been developed by using mucin-1 (MUC1), carcinoembryonic antigen and products of the *KRAS* gene as TAAs. Recently, TAAs over-expression in PDAC cells have been identified and used in vaccine therapies. One such TAA that is currently being used actively is mesothelin, effectively mediates $CD8^+$ T cell response [291,298,299].

4. Conclusion

Advances in the understanding of the different cancers at the molecular level have taken place enormously in the past few decades. The first generation of EGFR inhibitors showed that biomarker-based lung cancer therapy can result in an overall better patient outcome. Thus knowing the factors that correlate tumor shrinkage and/or tumor stability will help make a decision about the remedies to be adopted in future. Melanoma tumor antigen PRAME and glutathione-S-transferase (GST) should be investigated in breast cancer as a potential therapeutic target. Extensive research over the past decades on oral cancer research has only improved the quality of life in oral cancer patients but there is no significant advancement in the treatment. Successful oral cancer awareness must be planned since the predominant cause of oral cancer is smoking, alcohol consumption and chewing of betel quid with or without tobacco or areca nut. With the elucidation of the molecular basis of the disease, the pathways involved in the process are being elucidated. Targeting the signaling molecules in order to block the cascade has become a leading field for conducting future studies. The associations between chromosomal rearrangement and mutagen-induced mutations have been established but the precise mechanism of gene recombination induced by radiation is still unknown and needs to be uncovered. Mutational markers against a specific type of cancer have already been in use, however, more research and advancement are required in this field to develop accurate diagnostic processes. Understanding the mutational processes of cancer can be useful for the development of new targeted therapeutics against it. These targeted

therapies should be capable of extending life duration and assuring a good quality of life. Clinical trials are being conducted to decipher the toxicities associated with the use of single therapeutic drug and the combination of two or more drugs. Further research is needed to identify specific biomarkers which can predict the treatment efficacy. Recent studies proved that the more we understand the biology, the more we realize there might be a combination of genotoxic and non-genotoxic carcinogenesis at the level of initiation and promotion. We cannot design and develop efficacious diagnostics and therapeutics, if we do not understand the evolutionary sequence in time and space of multiple cancer types.

Contributions

P. P. conceived and wrote the article and display items. S.C. contributed to discussions of the content and writing of the article. P.P. and A.K.M. researched the data for the article. P. P., S. C. and A. K. M. reviewed and edited the article before submission.

Conflicts of interest

There are no conflicts of interest.

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