IJLSR (2018), Vol. 4, Issue 3 **Review Article**

IJLSR INTERNATIONAL JOURNAL OF LIFE SCIENCES AND REVIEW

Received on 08 February 2018; received in revised form, 18 March 2018; accepted, 28 March 2018; published 31 March 2018

GENE PATHWAYS IN CANCER: BEGINNING, ENDING AND THE ACTORS OF THE STORY

Mirza Jawad Ul-Hasnain[* 1, 2], Tehreem Anwar [1], Bakhtawar Afzal [2], Hafiz Muhammad Talha Malik [2, 3] and Syed Hassan Abbas [2]

Department of Bioinformatics [1], Virtual University, Lahore, Pakistan.
Department of Biosciences [2], COMSATS Institute of Information and Technology, Islamabad, Pakistan.
Jamilul Rehman Center for Genome Research [3], PCMD (ICCBS), University of Karachi, Karachi, Pakistan.

ABSTRACT: The advancements of cancer research if put in a nutshell can be described as: "Cancer is a genetic disease." From the past two decades, several actors for cancer are identified, their mutations are characterized, and the pathways they control are described. Intricate relations among JAK-STAT, TGF-B, MAPK, Ras, Wnt, Notch, and Hedgehog signaling pathway have a vital role in apoptosis, survival, proliferation, and differentiation. Dysregulation of these pathways due to driver mutations are often found involved in the growth of cancer. The purpose of this review is to enlighten the advancement in these areas of cancer, specify where there is room for research, and provide a potential base for future research.

Keywords: Cancer, Pathways, Tumorigenesis, Proliferation, Apoptosis, Oncogenes

Mirza Jawad Ul-Hasnain

Instructor, Department of Bioinformatics, Virtual University of Pakistan, D-102, Satellite Town, Rawalpindi, Pakistan.

E-mail: mirza.jawad@vu.edu.pk

INTRODUCTION: Information we already have: Cancer, a term that relates to the abnormal growth of any living physical entity that resides inside the body [1]. The entity can be a vessel, a tissue, or even a cell [2]. The term cancer is further divided into several major types, namely, the proliferation of cells, angiogenesis, vascular genesis, carcinogenesis, leukemia and lymphomas [3]. Several cancer hallmarks have been stamped for the recognition, working behaviour of cancerous cells and prevention protocols [4]. Some of them are known to sustain proliferative signaling or enabling replicative immortality evading over the growth Suppressors, even inducing angiogenesis ultimately resisting cell death, activating invasion and metastasis [5].In the case of developing an understanding of the intense behavior of the cancer-causing genes, gene pathway analysis is mandatorily important before the gene networks [6].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.IJLSR.4(3).35-47

The article can be accessed online on www.ijlsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.IJLSR.4(3).35-47

Based on the occurring frequency 20 genes are very vital in cancer study [7, 8]: TP53, XRCC1, PTGS2, EGFR, AKT1, TERT, VEGFA, TGFB1, mTOR, PTEN, MMP2, GSTM1, CXCR4, CTNNB1, CDH1, MYC, ABCB1, CDKN1A, ABCG2 and CCND1 **Table 1**. Prescribed network analysis shows that linkage of MYC, PTGS2, VEGFA, CXCR4, ABCB1, ABCG2, XRCC1, and GSTM1 genes are only hypothetically reported while rest 12 genes show experimental support in their network linkages. A panel of these 8 genes can be characterized experimentally using different assays including invasion assay [9], proliferation assay [10], adhesion assay [11,] and migration assays [9].

TABLE 1: LIST OF EXPERIMENTALLY CONNECTED AND HYPOTHETICAL GENES IN PRESCRIBED NETWORK

Experimentally connected	Hypothetical
Tumor protein p53(TP53)	V-myc avian myelocytomatosis viral oncogene homolog(MYC)
Matrix metallopeptidase 2 (MMP2)	Prostaglandin-endoperoxide synthase 2 (PTGS2)
Mechanistic target of rapamycin (mTOR)	Vascular endothelial growth factor A (VEGFA)
Epidermal growth factor receptor (EGFR)	C-X-C motif chemokine receptor 4(CXCR4)
AKT Serine/Threonine Kinase 1 (AKT1)	ATP Binding Cassette Subfamily B member 1(ABCB1)
Telomerase reverse transcriptase (TERT)	ATP Binding Cassette Subfamily G member 2(ABCG2)
Phosphatase and tensin homolog (PTEN)	X-ray repair cross-complementing 1(XRCC1)
Transforming growth factor beta 1(TGFB1)	Glutathione s-transferase mu 1(GSTM1)
Catenin beta 1(CTNNB1)	
Cadherin 1(CDH1)	
Cyclin-dependent kinase inhibitor 1A (CDKN1A)	
Cyclin D1(CCND1)	

Three types of genes, in the result of alterations, are accountable for the process of tumorigenesis; oncogenes, the tumor-suppressor genes, and the genes responsible for stability [12]. Single gene faults cannot tend to be alone responsible for causing cancer, unlike other diseases where single gene mutation can be a cause including cystic fibrosis or muscular dystrophy. Cells have several defenses that safeguard them from adverse effects of tumor responsible genes, and cancer only develop when multiple genes have mutations and alterations [13]. So, in this sense, we can say mutations in genes are cancer responsible, not cancer causing.

The mutations in tumor suppressor genes are somehow different from that occurring in oncogenes. Mutations lead to the reduction of gene product activity [14]. Such activations can be caused by several factors including truncated proteins as a result of mutations, the essentially required mutated crucial residues, epigenetic silencing or indels of various sizes. We can think of mutations of tumor suppressor genes to be malfunction brake in a vehicle where the vehicle continues to move even if the vehicle driver is attempting to engross it. The cancer repressor genes can employ a specific benefit on the cell when only one of the two alleles is dysfunctional, and the other is functional [15]. But, alterations in both paternal and maternal alleles are needed to deliberate that selective advantage [16].

Oncogenes mutations render them active in conditions under which wild type genes are not [17]. Activations of oncogenes can be due to alterations of several different types including translocations in chromosomes, amplification of genes or even from some intragenic mutations that lead to alter the important residues responsible for normal gene functioning [12]. For instance, alteration of valine to glutamate at codon 599 in BRAF gene leads to activation of kinase domain loop [18]. Active BRAF kinase leads to aberrant growth by the process of phosphorylating the targets present downstream, including the kinase regulated by extracellular signals [19]. Oncogene mutation is like an accelerator stuck in an automobile; the car does not stop moving even if the driver has removed his foot from it.

Stability genes have an opposite mechanism of mutations from tumor suppressor genes and oncogenes. All the repair mechanisms considering mismatch, base-excision, and nucleotide-excision repairs are included in this class of genes [20, 21, 22]. These genes are responsible for keeping alterations to a minimum, so their inactivation can lead to a very high mutation rate [23]. Same as in the case of cancer suppressor genes, both the maternal alleles and paternal alleles are required to be activated. In term of automobile analogy, we can think of stability genes as mechanics, and faulty genes are more like an incompetent mechanic. The mutations occurring in these three types of genes can be both somatic or germline. Examples of Inherited syndromes associated with these kinds of mutations are also listed in **Table 2**.

Major Pathways and Genes Involved in them: Research from the past decade shows that the number of pathways is way less than that of genes. The notion being very common for researchers that there is a collection of many such diverse types of genes that, when altered, produce similar or nearly similar phenotypes. So, it is preferred to study pathways rather than genes, and the same strategy is followed in this review.

TABLE 2: MOST OCCURRING GENES, RELATED SYNDROMES AND HEREDITARY PATTERNS, PATHWAYS (SINGLE PATHWAY SELECTED IS THE BEST GUESS MADE), HEREDITARY TUMOR TYPES IN WHICH THEY ARE PRESENT AND GROWTH FACTORS THEY ACTIVATE ARE LISTED

Gene	Syndrome	Hereditary pattern	Pathways	Major heredity tumor types	Growth factor activation
TP53	Li-Fraumeni Syndrome	Dominant	p53	Breast, sarcoma, adrenal, brain…	Cell cycle arrest, DNA repair and apoptosis [24, 25]
VEGFA	del22q11 syndrome/Crow-Fukase syndrome	Dominant	VEGFA-VEGFR2	Breast, bladder, colorectal, cervical, lung…	Angiogenesis, endothelial cell growth [26, 27, 28]
TGFB1	Aortic Aneurysms syndrome	Dominant	SMAD	Leukemia, liver, lung, breast, melanoma, ovarian, prostate…	Cell differentiation, apoptosis, cell growth, cell hemostasis, insensitivity to anti-growth signals [29, 30]
PTGS2	Cornelia-de Lange syndrome	Dominant	Arachidonic acid metabolism	Thyroid, skin, chronic lymphocytic leukemia, pancreatic…	Sustained angiogenesis [31, 32]
AKT1	Cowden and Cowden-like Syndromes	Predominant	PI3K-AKT	Ovarian, breast	Angiogenesis, increase in glucose metabolism[33]
CTNNB1	Beckwith-Wiedemann syndrome	Autosomal Dominant	APC	Colon, liver, medulloblastomas	Cell adhesion, proliferation, differentiation [34, 35]
MYC	WRN syndrome	Sex-linked Dominant	APC	Lymphomas, small cell lung cancer	cell proliferation [36, 37]
MMP2	Multicentric osteolysis and arthritis syndrome	Autosomal Dominant	GnRH	CNS tumors, breast, liver	Vascularization, metastasis [38]
CCND1	Myelodysplastic Syndromes (MDS)	Dominant	RB	Leukemias, breast, mantle cell lymphoma	Proliferation [39, 40]
TERT	Severe Acute Respiratory Syndrome (SARS)	Autosomal Dominant	?	glioma, neoplasms, melanoma	Immortality [41]
MTOR	Acute Coronary Syndrome	Dominant	mTOR	Breast, lung	Evading apoptosis [42, 43]
PTEN	Cowden Syndrome	Dominant	PI3K	Endometrial, glioblastoma, breast, prostate.	Apoptosis [44, 45]
EGFR	Hereditary lungs cancer syndrome	Dominant	RTK	Glioblastomas, non-small cell lung cancer	Proliferation[46]
CXCR4	WRN syndrome/ WHIM syndrome	Autosomal Dominant	cytokine-cytokine receptor interaction	Breast, pancreatic, lung, neoplasms	Cardiovascular organogenesis, metastasis, apoptosis[47]
ABCB1	acute coronary syndrome	Multifactorial	ABC transporter	Breast, lung, cervical, thyroid	Resistance to chemotherapy[48]
CDKN1A	Familial Malignant	Autosomal Dominant	Cell cycle	Melanoma, pancreas	Proliferation49
XRCC1	Polycystic ovary syndrome	Autosomal Dominant	BER	Gliomas, brain and CNS tumors	DNA repair[50]
GSTM1	Coronary artery disease	?	Metabolism of xenobiotics by cytochrome p450	ALL Prostate, lung, bladder, colorectal, breast…	Premalignant Lesions[51]
ABCG2	Junior blood group	Recessive	ABC transporter	Breast, lung, pancreatic, ALL, osteosarcoma	Proliferation[52]
CDH1	Hereditary diffuse gastric cancer syndrome	Autosomal Dominant	APC	Gastric, breast, stomach	Apoptosis [53, 54]

Receptor Tyrosine Kinase RTK Pathway: In human cancers at codon number 599 if a mutation occurs to change valine to glutamate in BRAF gene leads to activation of kinase domain loop[18] known to be regulated by the process of Ser601 and Thr598 phosphorylation [55]. This advocates that substitution of glutamate to valine at codon number 599 impersonates a phosphate group. That is why this substitution constitutively activates the enzyme even when signals are not present that would, in a normal situation, phosphorylating the adjacently existing serine or threonine residues. This activation of the BRAF kinase domain is ultimately followed by phosphorylation of certain downstream

entities [19] such as extracellular signal-regulated kinase (ERK) that leads to abnormal growth **Fig. 1**.

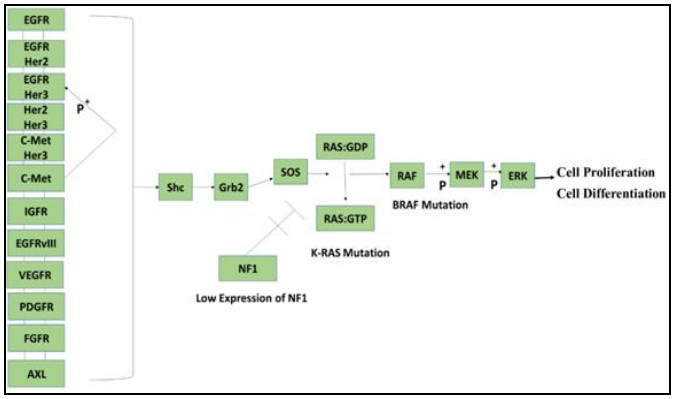

FIG. 1: RECEPTOR TYROSINE KINASE (RTK) PATHWAY. 'GPG' denotes growth-promoting-genes-which means, genes that enhance cell growth or proliferation or hinder the speed of cell arrest or death. Diamonds and adjacent textboxes indicate PPIs. T-bars indicate transcriptional repression. $^{+}$P represent covalently attached phosphate groups.

RB Pathway: Phase shift from the resting phase to replicating stage of the cell cycle (*i.e.*, from G0 or G1 phase to S phase), is sometimes directly controlled by some cancer genes **Fig. 2**. Proteins which are the result of such genes are as heterogenous as Rb (transcription factor), cdk4, cyclin D1 (which cooperates with and activate cdk4) and p16 (which cooperates with and constrain cdk4) [56, 57, 58]. Mutation activates the genes (oncogenes) that code for cyclin D1 and cdk4 while inactivating the genes (tumor suppressor) that code for p16 and Rb [59].

Additionally, with studying of functional systems through modeling, convincing proves has also been established by the comprehensive study of individual tumors illustrating that these under discussion four genes have roles in a common human cancer pathway [60]. Research has found out that the mutations that occur in this pathway follow the rule of exclusivity, meaning that only one of these gene mutations causes tumor, provided that functional consequences of each mutation were analogous [56, 57, 58, 59, 60, 61].

P53 Pathway: TP53 gene that encodes P53 protein [62] is a transcription factor which generally functions to restrict cell growth, and when induction of cellular stress takes place, cell death is stimulated by p53 [63, 64]. Missense point mutation is the most usual way that disrupts the p53 pathway that hinders its ability to bind with its specific allied recognition sequence [65]. Several other triggers can also achieve the same effect such as MDM2 geneamplification[66] and DNA tumor virus's infection, which inactivates the pathway by inhibiting products such as E6 protein that binds to p53 pathway [67] **Fig. 3**.

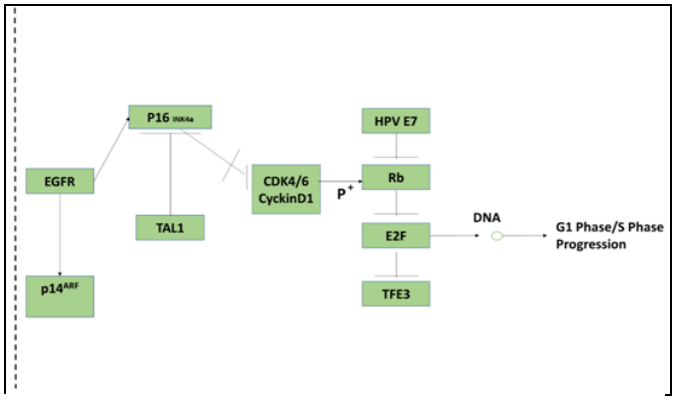

FIG. 2: Rb PATHWAY. SIGNS AS EXPLAINED IN FIG. 1

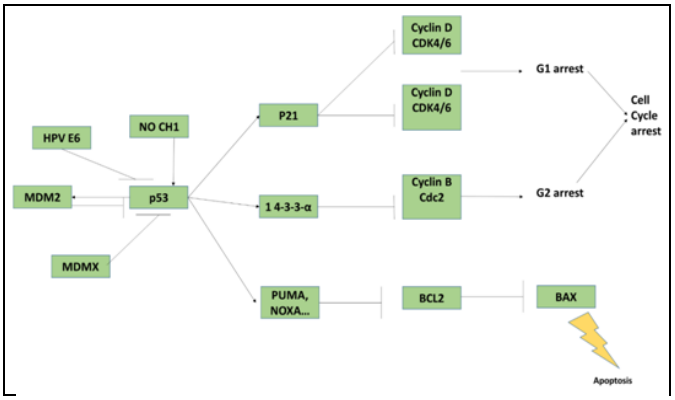

FIG. 3: P53 PATHWAY SIGNS AS EXPLAINED IN FIG. 1

APC Pathway: APC gene is a tumor suppressor gene whose mutation causes β-catenin to accumulate, which then bind to T cell factor-4. Transcriptional activation of some unknown genes is activated by this binding of β-catenin to Tcf-4. c-MYC oncogene being the target gene identified in this signaling pathway, where wild type APC downregulates its expression and is activated by β-catenin. The effects are mediated by the Tcf-4 binding sites that are present in c-MYC promoter [65, 66].

PI3K Pathway: Epidermal Growth Factors Receptor, abbreviated as EGFR is a transmembrane glycoprotein and is a member of Superfamily, a tyrosine kinase receptor [68]. An EGRF signaling pathway is a key pathway that is discussed for the survival, differentiation, proliferation, and growth

regulation in mammalians cells [69]. The role of Akt1 with EGRF during the cellular response to any oxidant quibble/injury was investigated in this approach. It was known that PI3k phosphorylates and activates Akt1, upregulating for the evading apoptosis process but in normal conditions [70]. We found that EGFR signaling provokes the apoptosis activity by suppressing Akt1 and the de-phosphorylation of EGFR resulting in the expression of the Akt1 and the survival of the cell growth and the raised Akt activity advises defense against oxidative stress-induced apoptosis [71].

PI3k/AKT1 and MTOR and Antagonistic Behaviour of PTEN: The mammalian target of rapamycin mTOR, is known to be a key gene in the evading apoptosis mechanism [72] but when required participates as a usual process in normal cell life. It plays the role of downstream effector in PI3k/AKT1 pathway [73]. A mTOR signaling pathway is activated by PI3k-Akt signaling k2 pathway activated by the Cytokine-cytokine receptor interaction on the ECM [74]. As a finding of studies, we know that PI3k. AKT/mTOR pathway is a signaling pathway that intracellularly plays a vital role in cell cycle regulation [75]. This pathway is directly responsible for the proliferation, cellular quiescence, cancer, and even the longevity [76]. Activation of PI3K from the signals coming from the ECM phosphorylates and activates the AKT, confining it in the plasma membrane. AKT has many pathways, for example, inhibition of p27 [77], activation of CREB [78], activating Ptdlns-3ps [79], confining of FOXO in the cytoplasm [80], activating mTOR which can further affect the transcription of p70 or 4EBP1 [81]. These pathways are disturbed by numerous factors, which influence to harvest cancer. These factors include PTEN, HB9 and GSK3B, *etc* [82, 83, 84].

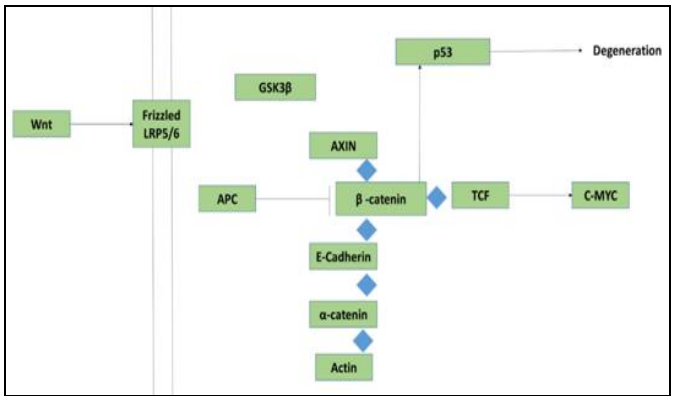

FIG. 4: APC PATHWAY. SIGNS AS EXPLAINED IN FIG. 1

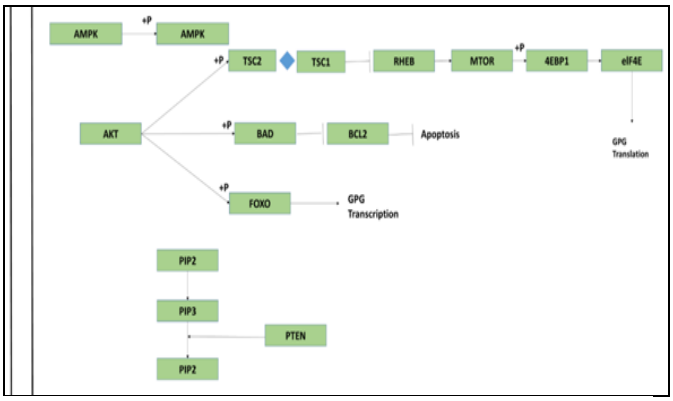

FIG. 5: PI3K PATHWAY SIGNS AS EXPLAINED IN FIG. 1

SMAD Pathway: Transforming growth factor (TGFβ) is a key gene involved in this pathway that targets SMAD proteins and some other proteins those results in dysregulations [84, 85]. TGFβ has a broad number of activities including stimulation of cell proliferation [85], context-specific inhibition [86], extracellular matrix ECM production and degradation [87], mediating the cell responses that occur in defense of an injury [88] and direction of carcinogenesis [89]. Following several phosphorylation and activation events, TGFβ acts on SMAD proteins, and a complex is formed which acts as a transcriptional regulator of target genes [90]. We have discussed only pathways so far. Within these pathways, some genes are very important when we talk about cancer. Their importance and role in the pathways mentioned above are discussed in detail below.

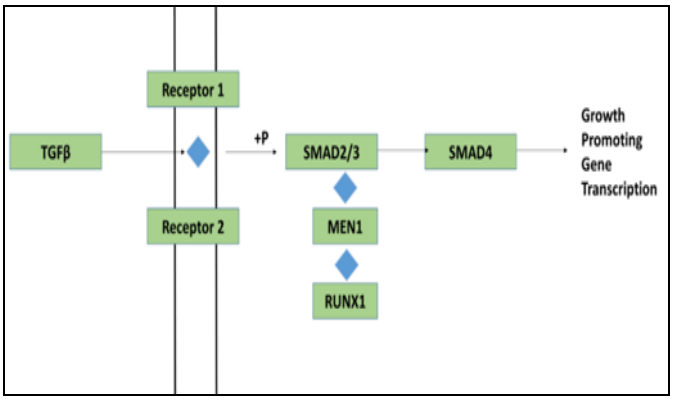

FIG. 6: SMAD PATHWAY. SIGNS AS EXPLAINED IN FIG. 1

Akt1 and CTNNB1: Talking of Akt and CTNNB1 interaction we found that CTNNB1 (beta-catenin 1) is a key gene and main effector in the Wnt signaling pathway in stem cells as well as embryonic cell development and tumorgenesis

mechanism [91]. Beta-catenin signaling pathway includes the adhesion of the cells onto the ECM, whereas, a mutation in beta-catenin results in invasion and metastasis [5]. Wnt signaling pathways comprises of a group of signal transduction passageways made up of those proteins that allow the signals to pass inside from the cell surface *via* receptors located on cell surface [92]. Akt (protein kinase B or PKB) present in Wnt like PI3K-Akt pathway for the transduction of the signals to promote the growth and survival when receiving the extracellular signals. Mostly Akt makes beta-catenin to get phosphorylated results in 14-2- 3zeta binding and stabilizes the CTNNB1 for the development of stem cells [93].

Akt1 and PTEN: PTEN (Phosphatase and tensin homolog) is a significant gene in humans. Its mutation can cause many cancers in Homo sapiens. Its lost copy has reported 70% of the prostate cancer cases [94]. It is known to be a tumor suppressor gene [95] and has always been under consideration in cancer biology. Akt signal transduction pathway is reported as in an equilibrium that is altered by mutated tumor suppressor genes like PTEN and causes not to go the apoptosis process, which leads to cancer [96].

Akt1, TERT, Tp53, and MDM2: Telomerase reverse transcriptase TERT, is a catalytic part of a telomerase unit of an enzyme [97]. The addition of telomere repeats is made possible by telomerase, as TTAGGG and comprises of a protein subunit for the reverse transcription activity being a reverse transcriptase [98]. The telomere is a region which stops the cell division after a certain time [99] and undergoes apoptosis process while TERT elongates the telomere region by adding repeated units making a cell immortal [100]. Tp53 is known as a tumor suppressor as its function is to go for the apoptosis mechanism in case of the DNA damage or breakdown [95, 96, 97, 98, 99, 100, 101].

Mouse double minute 2 homolog, MDM2 is a regulator attached to tp53 which controls tp53 whether to allow it to go for apoptosis or not in normal condition [102]. If any DNA damage happens, tp53 sends a signal to MDM2 to get suppressed so that tp53 can be up-regulated and apoptosis process can be gone through. But due to the mutation in tp53 suppression, ofMDM2 is disabled, and no apoptosis occurs, which results in cancer. This mutated tp53 enhances TERT activity and cause oncogenesis and in this downstream TERT suppress Akt1 to increase tumor genesis and reduced evading apoptosis [94, 96, 97, 98, 99, 100, 101, 102, 103]. TERT regulates CTNNB1 *via* BRG1 too[104].

AKt1 and VEGFA: Vascular endothelial growth factor VEGF is a signal protein that stimulates the processes which are integral for differentiation and proliferation of the cells, namely, angiogenesis and vascular genesis [105]. But the excessive angiogenesis and vascular genesis cause tumor and cancer. But as we know that the normal function of PI3-Akt1 is to go for the cell destruction *via* mTOR signaling pathway when DNA abnormality occurs but in a normal manner [106]. At normal condition phosphorylation of AKT1 helps in the phosphorylation of VEGFA-R for the VEGFA mediated as activation but when a mutation in VEGF cause tumorigenesis by the excessive angiogenesis Akt1 down regulates VEGFA to suppress tumor [68, 107].

CTNNB1 and CDH1: E-cadherin or CDH1 is a key protein playing an integral role in cellular adhesion, and a decreased expression of this protein increases angiogenesis and cell invasiveness [108]. β-catenin is an essential constituent of the signaling pathway of Wnt [109] and gets combined with CDH1and the complex of these two proteins stabilize the cellular adhesiveness [110].

EGFR and CTNNB1 and CDH1: EGFR (Epidermal growth factor receptor) which inhibits Akt1 [111] from apoptosis upregulates CTNNB1 for the cellular adhesion supported by the Wnt pathway where CTNNB1 makes a complex with CDH1 [112]. EGRF and CTNNB1 both regulate each other to decrease invasion and metastasis. But CDH1 downregulates the overexpression of EGFR to avoid cancer [113]. Where interaction of nuclear PTEN (Phosphatase and tensin homolog) with APC indorses APC connotation with CDH1, and thus boosts the activity of cancer-suppression of APC-CDH1 complex [114]. PTEN also suppresses CTNNB1 and down-regulates its activity of cellular adhesion to increase the invasion and metastasis [115].

MMP2/TGFB1/Tp53 Downstream: TGFB1 (Transforming growth factor beta1) is involved in

certain essential cellular activities and functions like apoptosis, cell growth, and cell differentiation in both adults and embryo [116]. There is another significant gene MMP2 (Matrix metalloproteinase-2), which makes the breakdown of the ECM (extracellular matrix) in normal physiological conditions such as in reproduction or development of embryo [117].

The mutation in MMP2 causes metastasis as the ECM rapidly destroys and allows the cells to get out from it and spread apart [118]. We investigated from the literature that mutated MMP2 downregulates TGFB1 for the sustained angiogenesis process *via* VEGF signaling pathway. We also examined that there is a positive correlation between betweenTp53 and TGFB1 [116].

Tp53 and XRCC1: TP53 and X-ray repair cross-complementing protein 1 abbreviated as XRCC1, a DNA fixing and a tumor suppressor, respectively, underwrite to cancer progression [119, 120]. Whereas, the TP53 gene somehow may root the distinction in vulnerability to cancer, giving rise to clues about the progression of the disease. It's known that most of the genes that play their parts in DNA repair, such asXRCC1, are carrying the genetic metastasis which ultimately becomes the reason of changes in the DNA repairing ability and also change the exposure of the body to several fatal tumors, such as breast cancer [121, 122].

CTNNB1 and PTGS2/COX-2: Cytoplasmic beta-catenin is found to be linked with COX-2 overexpression for cell-cell adhesion [123]. Besides its function in cell adhesion and Wnt signaling pathway, an explicit RNA motif at 3'UTR of mRNA of COX-2 is recognized by β-catenin, and it interacts with HuR in the case of colon cancer [124].

PKM/AKT, PTEN, MDM2, Tp53, mTOR and TERT Linkage: By the phosphorylation of PKM/KT *via* PDK1 starting from the activation of PI3K, PTEN acts as a suppressor of the Akt1 pathways here. PKB/Akt supports the cell growth by inhibition of apoptosis activating MDM2 which can stop Tp53 [125] and then mTOR which on its behalf when victimized by any mutation causes tumor growth [126] which enhances TERT to elongate the telomere end sizes leading to tumors and cancer formation [4, 104, 126].

Tp53 and PTGS2/COX-2: The DNA damage induction by nitrogen and oxygen species activates Tp53, which in return musters NF-kappa-B to stimulate COX-2, ultimately following by consequences that are anti-apoptotic and cause the expansion of cells in the inflammatory precursor lesions [127]. The oncogenic stress that occurs due to initiation of growth-stimulating kinases upregulates COX-2 promoter being independent of NF-kappa-B and p53, working together with mutation of TP53 leading to the promoted tumor development [128].

Information that is needed To Know:

The Initiation: A mutation in the gatekeeping pathway initiates tumorigenesis in stem cell or the descendants of it that are partially differentiated, also known as a replication-competent cell that leads it to some growth factor activation [129]. Gatekeeping pathways are identified in some cancers like RB1, NF1, and APC in the eye, colon, and nervous system cancers, respectively [130]. However, the gatekeeper is not known in most of the cases. For example, if we talk about bladder, prostate, breast, lung or brain cancer, they can either be initiated by only one gatekeeping pathway or by any one of several gatekeeping pathways [131, 132, 133]. Several gatekeeping pathways and gatekeepers are recognized through the study of several uncommon families with particular types of cancer pre-disposition [16].

In the future, other families may also provide insights into the nature of gatekeeping pathways. The prediction is, however, that identification of novel gatekeeping genes will be through sequence identification of major cancer genome portion and more brute force approaches [134]. As central clues about pathogenesis and biology of cancer are provided by identification of gatekeeping mutations, so they are of fundamental importance in therapeutic and diagnostic strategies, and research on this subject should be prioritized [135].

The Actors: It seems that to achieve malignant status, cancer cells must gather several mutations in replication-competent cells. Cancer prevalence will be minimal if such mutations have to simultaneously occur in a single cell [136]. According to existing dogma, these mutations prevail slowly with time, where each mutation is producing

expansion clonally creating a new substrate for the upcoming mutations [137]. Are only normal mutations, along with clonal expansion, adequate for causing cancer or genetic instability is fundamental in the prevalence of cancer? This is a hotly debated issue [138, 139] but some facts are clarified through the research of the last ten years.

Firstly, the mutation rate is not very high in most of the cancers [140]. Typically, mutations in cancer cells are less than 1 megabase of DNA just like the probability of mutation in a normal cell which has conceded overpopulation bottlenecks and generations [141]. Secondly, genetic instability has a contribution to cancer prevalence as hereditary cancers, which are caused by flaws of tumor genes [141] **Table 1**.

In nonhereditary tumors, these facts argue against the common role of NER, BER, or MMR. However, another type of instability, namely Chromosomal instability CIN happens more in the prevailing types of cancers, and this instability is not determined at the nucleotide level, instead of at gross chromosomal level [142]. Although a small number of cases are studied for the actual rate of chromosomal changes, in nearly all solid tumors, aneuploidy, which is the result of chromosomal changes is observed [143]. Loss of heterozygosity is observed as chromosomal losses occur at the molecular level. 25% to 30% alleles exist in normal cells are lost due to chromosomal losses in cancer, and sometimes the sells lose over 75% of its alleles [142]. Both classic and modern studies confirm these facts [144, 145].

Such chromosomal losses can be beneficial for cancer cells allowing them to cause cancer by eliminating tumor suppressor gene and production of variants. The fundamental processes underlying CIN and aneuploidy in tumors are still largely needed to identify, but some candidate genes pathways and genes are proposed such as those involved in telomere crisis, centrosomes or cell cycle checkpoints [137, 146, 147, 148, 149, 150]. Telomerase is potentially important in the incidence of most cancers, which are age-dependent [148, 151]. The identification of molecular processes responsible for the genetic instabilities is an important area of study as these instabilities seems to be playing a pivotal role to cancer development and may lie the production of increased chemotherapeutic agents resistance [136, 138].

The Finishing: Most of the variations in cancer genes happen initially in the disease progression and are not recognized to be particularly linked with the change over the stage of the disease [152], although variations in tumor genes listed in **Table 1** are significant sponsors of cancer. Satellite lesions and seeding in other organs is the final stage that is majorly responsible for neoplastic deaths [153]. Early tumors can be excised by surgery, but lesions that are widely spread cannot be removed, and sometimes a milestone to be achieved in terms of treatment.

Some processes involved in early metastasis have been well studied till now such as the production of matrix-degrading protease and increased cell motility [154], through genetic changes responsible for bringing cells to this stage are still not identified. Evolution of cancer cells does not halt just as macroevolution never halts and new alternatives are always being creating with greater ability to metastasize and invade cells. As explained above, the evolution itself is caused by hereditary genetic variabilities [155]. However; this perspective of genetic changeover cannot be confirmed or nullified until we have a detailed knowledge of the mentioned genetic changeover processes.

Concluding Remarks: The three major milestones that are expected to occupy the emerging cancer research are (1) Discovery of novel genes that play roles in initiation and termination of tumor process and have a causal role in neoplasia. (2) Identification of gene pathways via which they act. (3) Paving new paths through his knowledge for the welfare and improvement of patients. The first two landmarks are expected to be achieved very recently, keeping in view the advances in cancer research technologies.

These advancing technologies are likely to proceed apace. Sooner genome of human will be in proper, refined shape, and road maps provided by previous studies are sufficient for researchers to follow conditioning that the novel genes are known. There will be a lot of genes, a lot of proteins and a lot of functions to consider. Also, as described above,

cancer molecular and cancer biology has not been kept up, and there is a need to separate them. The third challenge listed above is the most difficult to achieve. It is to provide actual benefits to patients. Road maps are hard to found. Excising billions of tumor cells is an intimidating task. Also, each of these cells is capable of speedy evolution and creating variants that resist chemotherapeutic agents [156, 157].

Cancer is no longer an unexplored mystery now. Knowing that a limited number of mutations in a few pathways can cause disasters, targeting those findings in the drug discovery can make wonders. But developing these next-generation drugs would be enough for minimizing cancer mortality in the long term? The western societies enjoying less morbidity rate is due to better prevention not better cure. Preventive measures can help restrain from the disease, such as limiting the exposure to carcinogens such as cigarette smoke, sunlight *etc*.[158]. Early detection of cancer can result in less mortality rate, for example, colon, breast, and prostate cancer.

Moreover, 30 to 40 years are needed to gather all the alterations necessary to progress to metastatic disease [159]. This allows detection of cancers at that stage where cure is possible. In fact, this knowledge will pave a path to the development of new generation drugs, tests and employing target-specific imaging that will make detection of cancers at early stage possible [160, 161]. Though less theatrical than cures, early detection and prevention are most feasible means to reduce cancer deaths.

ACKNOWLEDGEMENT: Nil

CONFLICT OF INTEREST: Nil

REFERENCES:

1. Miller AB, Hoogstraten B, Staquet M and Winkler A: Reporting results of cancer treatment. Cancer 1981; 47(1): 207-214.
2. Warburg O: On the origin of cancer cells. Science 1956; 123(3191): 309-314.
3. Tibshirani R, Hastie T, Narasimhan B and Chu G: Diagnosis of multiple cancer types by shrunken centroids of gene expression. Proceedings of the National Academy of Sciences 2002; 99(10): 6567-6572.
4. Tallerico R, Garofalo C and Carbone E: A new biological feature of natural killer cells: the recognition of solid tumor-derived cancer stem cells. Frontiers in Immunology 2016; 7: 179.
5. Hanahan D and Weinberg RA: Hallmarks of cancer: the next generation. Cell 2011; 144(5): 646-674.
6. Waugh DJ and Wilson C: The interleukin-8 pathway in cancer. Clin Can Res 2008; 14(21): 6735-6741.
7. Calin GA, Sevignani C, Dumitru CD, Hyslop T, Noch E, Yendamuri S and Croce CM: Human micro RNA genes are frequently located at fragile sites and genomic regions involved in cancers. Proceedings of the National academy of Sciences of the United States of America 2004; 101(9): 2999-3004.
8. Lengauer C, Kinzler KW and Vogelstein B: Genetic instabilities in human cancers. Nature 1998; 396(6712): 643.
9. Ma L, Teruya-Feldstein J and Weinberg RA: Tumour invasion and metastasis initiated by microRNA-10b in breast cancer. Nature 2007; 449(7163): 682.
10. Singh SK, Clarke ID, Terasaki M, Bonn VE, Hawkins C, Squire J and Dirks PB: Identification of a cancer stem cell in human brain tumors. Cancer Research 2003; 63(18): 5821-5828.
11. Taichman RS, Cooper C, Keller ET, Pienta KJ, Taichman NS and McCauley LK: Use of the stromal cell-derived factor-1/CXCR4 pathway in prostate cancer metastasis to bone. Cancer Research 2002; 62(6): 1832-1837.
12. Vogelstein B and Kinzler KW: Cancer genes and the pathways they control. Nature medicine 2004; 10(8): 789.
13. Sugimura T, Terada M, Yokota J, Hirohashi S and Wakabayashi K: Multiple genetic alterations in human carcinogenesis. Environmental Health Perspectives 1992; 98: 5.
14. Sager R: Tumor suppressor genes: the puzzle and the promise. Science 1989; 246(4936): 1406-1412.
15. Santarosa M and Ashworth A: Haploinsufficiency for tumor suppressor genes: when you don't need to go all the way. Biochim Biophys Acta 2004; 1654: 105-122.
16. Knudson AG: Cancer genetics. Am J Med Genet 2002; 111: 96-102.
17. Hunter T: Cooperation between oncogenes. Cell 1991; 64(2): 249-270.
18. Davies H: Mutations of the BRAF gene in human cancer. Nature 2002; 417: 949-954.
19. Wan PT, Garnett MJ, Roe SM, Lee S, Niculesco-Duvaz D, Good VM, Jones CM, Marshall CJ, Springer CJ, Barford D and Marais R: Mechanism of activation of the RAF-ERK signaling pathway by oncogenic mutations of B-RAF. Cell 2004; 116: 855-867.
20. Vasen HF, Watson P, Mecklin JP and Lynch HT: New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC. Gastroenterology 1999; 116(6): 1453-1456.
21. Cheng L, Spitz MR, Hong WK and Wei Q: Reduced expression levels of nucleotide excision repair genes in lung cancer: a case-control analysis. Carcinogenesis 2000; 21(8): 1527-1530.
22. Hung RJ, Hall J, Brennan P and Boffetta P: Genetic polymorphisms in the base excision repair pathway and cancer risk: a HuGE review. American Journal of Epidemiology 2005; 162(10): 925-942.
23. Friedberg EC: DNA damage and repair. Nature 2003; 421: 436-440.
24. Yin Y, Stephen CW, Luciani MG and Fåhraeus R: p53 Stability and activity are regulated by Mdm2-mediated induction of alternative p53 translation products. Nat Cell Biol 2002; 4(6): 462-467.
25. Marcel V, Perrier S, Aoubala M, Ageorges S, Groves MJ, Diot A, Fernandes K, Tauro S and Bourdon JC: Δ160p53

is a novel N-terminal p53 isoform encoded by Δ133p53 transcript. FEBS Lett 2010; 584(21): 4463-8.
26. Amaro A, Guerra AB, Defino MP, Vieira LA, Peluso C, Bianco B and Rodrigues LM: Vascular endothelial growth factor gene variations as a risk predictor in disc degeneration. Einstein 2017; 15(4): 403-408.
27. Naykoo NA: Single nucleotide polymorphisms, haplotype association and tumor expression of the vascular endothelial growth factor (VEGF) gene with lung carcinoma. Gene 2017; 608: 95-102.
28. Lohela M: VEGFs and receptors involved in angiogenesis versus lymphangiogenesis. Curr Opin Cell Biol 2009; 21: 154-165.
29. Vitiello GAF: Transforming growth factor beta 1 (TGFβ1) polymorphisms and haplotype structures have dual roles in breast cancer pathogenesis. J Cancer Res Clin Oncol 2018; 144: 645.
30. Zuo ZK: TGFβ1-Induced LncRNA UCA1 Promotes Gastric Cancer Invasion and Migration. DNA Cell Biol 2017; 36(2): 159-167.
31. DE-Cremoux P, Hamy AS, Lehmann-Che J, Scott V, Sigal B, Mathieu MC, Bertheau P, Guinebretière JM, Pierga JY, Giacchetti S, Brain E, Marty M, Asselain B, Spyratos F and Bièche I: COX2/PTGS2 expression is predictive of response to neoadjuvant celecoxib in HER2-negative breast cancer patients. Antican Res 2018; 38(3): 1485-90.
32. Liao X: Prokaryotic expression, purification and characterization of human cyclooxygenase-2. International Journal of Molecular Medicine 2017; 40(1): 75-82.
33. Orloff MS: Germline PIK3CA and AKT1 mutations in cowden and cowden-like syndromes. American Journal of Human Genetics 2013; 92(1): 76-80.
34. Yu W, Li L, Zheng F, Yang W, Zhao S, Tian C, Yin W, Chen Y, Guo W, Zou L and Deng W: β-Catenin cooperates with creb binding protein to promote the growth of tumor cells. Cell Physiol Biochem 2017; 44: 467-478.
35. Yang W, Ning N and Jin X: The lncRNA H19 Promotes cell proliferation by competitively binding to miR-200a and derepressing β-Catenin expression in colorectal cancer. Biomed Res Int 2017; 2767484.
36. Bretones G, Delgado MD and León J: Myc and cell cycle control. Biochimicaet Biophysica Acta (BBA) - Gene Regulatory Mechanisms 2015; 1849(5): 506-516.
37. Wahlström T and Henriksson MA: Impact of MYC in regulation of tumor cell metabolism. Biochim Biophys Acta 2015; 1849(5): 563-569.
38. El-Bizri N: SM22α-Targeted deletion of bone morphogenetic protein receptor ia in mice impairs cardiac and vascular development and influences Organogenesis. Development (Cambridge, England) 2008; 135(17): 2981-2991.
39. Sun G: Decreased MiR-17 in glioma cells increased cell viability and migration by increasing the expression of Cyclin D1, p-Akt and Akt. PLoS One, 2018; 13(1): e0190515.
40. Ortiz AB, Garcia D, Vicente Y, Palka M, Bellas C and Martin P: Prognostic significance of cyclin D1 protein expression and gene amplification in invasive breast carcinoma. PLoS One, 2017; 12(11): e0188068.
41. Ahmad F, Patrick S, Sheikh T, Sharma V, Pathak P, Malgulwar PB, Kumar A, Joshi SD, Sarkar C and Sen A: TERT-EZH2 network regulates lipid metabolism and DNA damage responses in glioblastoma. J Neurochem 2017; 143(6): 671-683.
42. Meng D, Frank AR and Jewell JL: mTOR signaling in stem and progenitor cells. Development 2018; 145.
43. Houssaini A and Adnot S: mTOR: A key to both pulmonary vessel remodeling and right ventricular function in pulmonary arterial hypertension? American J of Respiratory Cell and Mol Biol 2017; 57(5): 509-11.
44. Ma J: PTEN Gene Induces Cell Invasion and Migration via Regulating AKT/GSK-3β/β-catenin signaling pathway in human gastric cancer. Dig Dis Sci 2017; 62: 3415.
45. Reed DE and Shokat KM: INPP4B and PTEN Loss Leads to PI-3, 4-P2 Accumulation and Inhibition of PI3K in TNBC. Mol Cancer Res 2017; 15(6): 765-775.
46. Baal JV, Widt JD, Divecha N and Van-Blitterswijk WJ: Diacylglycerol kinase θ counteracts protein kinase C-mediated inactivation of the EGF receptor, The International Journal of Biochemistry and Cell Biology 2012; 44(11): 1791-1799.
47. Chatterjee S, Azad BB and Nimmagadda S: The intricate role of CXCR4 in Cancer. Advances in Cancer Research 2014; 124: 31-82.
48. Sui H, Fan ZZ and Li Q: Signal transduction pathways and transcriptional mechanisms of ABCB1/ Pgp-mediated multiple drug resistance in human cancer cells. J Int Med Res 2012; 40(2): 426-35.
49. Kreis NN et al.: Mitotic p21Cip1/CDKN1A is regulated by cyclin-dependent kinase 1 phosphorylation. Oncotarget, 2016; 7(31): 50215-50228.
50. Wei L: Damage response of XRCC1 at sites of DNA single-strand breaks is regulated by phosphorylation and ubiquitylation after degradation of poly (ADP-ribose). Journal of Cell Science 2013; 126(19): 4414-4423.
51. Zhang ZX and Zhang Y: Glutathione S-transferase M1 (GSTM1) null genotype and coronary artery disease risk: a meta-analysis. Int J Clin Exp Med 2014; 7(10): 3378-84.
52. Wieckhusen C, Rink G, Scharberg EA, Rothenberger S, Stürtzel A, Richter E and Bugert P: A new genetic background for the Jr(a-) blood group phenotype caused by the ABCG2*439T allele encoding a p.Arg147Trp change. Transfusion 2017; 57(12): 3063-3064.
53. Van der Post RS: Hereditary diffuse gastric cancer: updated clinical guidelines with an emphasis on germline CDH1 mutation carriers. Journal of Medical Genetics 2015; 52(6): 361-374.
54. Huang J, Ikeuchi Y, Malumbres M and Bonni A: A Cdh1-APC/FMRP ubiquitin signaling link drives mGluR-dependent synaptic plasticity in the mammalian brain. Neuron 2015; 86(3): 726-739.
55. Zhang BH and Guan KL: Activation of B-Raf kinase requires phosphorylation of the conserved residues Thr598 and Ser601. The EMBO Journal 2000; 19(20): 5429-5439.
56. Sherr CJ: Cancer cell cycles revisited. Cancer Res 2000; 60: 3689-3695.
57. Ortega S, Malumbres M and Barbacid M: Cyclin D-dependent kinases, INK4 inhibitors and cancer. Biochim Biophys Acta 2002; 1602: 73-87.
58. Classon M and Harlow E: The retinoblastoma tumor suppressor in development and cancer. Nat Rev Cancer 2002; 2: 910-917.
59. Serrano M, Hannon GJ and Beach D: A new regulatory motif in cell-cycle control is causing specific inhibition of cyclin D/CDK4. Nature 1993; 366(6456): 704.
60. Sherr CJ and McCormick F: The RB and p53 pathways in cancer. Cancer Cell 2002; 2(2): 103-112
61. Ichimura K: Deregulation of the p14ARF/MDM2/p53 pathway is a prerequisite for human astrocytic gliomas with G1-S transition control gene abnormalities. Cancer Res 2000; 60: 417-424.
62. Vogelstein B, Lane D and Levine AJ: Surfing the p53 network. Nature 2000; 408: 307-310.

63. Oren M: Decision making by p53: life, death and cancer. Cell Death Differ 2003; 10: 431-442.
64. Prives C and Hall PA: The p53 pathway. J Pathol 1999; 187: 112-126.
65. He TC, Sparks AB, Rago C, Hermeking H, Zawel L, Da Costa LT, Morin PJ, Vogelstein B and Kinzler KW: Identification of c-MYC as a Target of the APC Pathway. Science 1998; 281(5382): 1509-1512.
66. Seshacharyulu P, Ponnusamy M, Haridas D, Jain M, Ganti A and Batra S: Targeting the EGFR signaling pathway in cancer therapy. Expert Opinion on Therapeutic Targets 2013; 16(1): 15-31.
67. Oda K, Matsuoka Y, Funahashi A and Kitano H: A comprehensive pathway map of epidermal growth factor receptor signaling. Mol Syst Biol 2005; 1(1): E1-E17.
68. Reifenberger G, Liu L, Ichimura K, Schmidt EE and Collins VP: Amplification and overexpression of the MDM2 gene in a subset of human malignant gliomas without p53 mutations. Cancer Research 1993: 53(12): 2736-2739.
69. Butz K, Shahabeddin L, Geisen C, Spitkovsky D, Ullmann A and Hoppe-Seyler F: Functional p53 protein in human papillomavirus-positive cancer cells. Oncogene 1995; 10(5): 927-936.
70. Kim KY and Lee JH: Apoptotic effect in combination of cyclosporin A and taxol on oral squamous cell carcinoma cell line through the PI-3 kinase/Akt1 Pathway. Journal of the Korean Association of Oral and Maxillofacial Surgeons 2007; 33(5): 426-436.
71. Wang X, McCullough KD, Franke TF and Holbrook NJ: Epidermal growth factor receptor-dependent Akt activation by oxidative stress enhances cell survival. Journal of Biological Chemistry 2000; 275(19): 14624-31.
72. Porta C, Paglino C and Mosca A: Targeting PI3K/ Akt/ mTOR signaling in cancer. Frontiers in Oncology 2014; 4: 64.
73. Pópulo H, Lopes JM and Soares P: The mTOR signaling pathway in human cancer. International Journal of Molecular Sciences 2012; 13(2): 1886-1918.
74. Sekulić A, Hudson CC, Homme JL, Yin P, Otterness DM, Karnitz LM and Abraham RT: A direct linkage between the phosphoinositide 3-kinase-AKT signaling pathway and the mammalian target of rapamycin in mitogen-stimulated and transformed cells. Cancer Research 2000; 60(13): 3504-3513.
75. Vara JÁF, Casado E, de Castro J, Cejas P, Belda-Iniesta C and González-Barón M: PI3K/Akt signaling pathway and cancer. Cancer Treatment Reviews 2004; 30(2): 193-204.
76. Zhang XL, Jia Q, Lv L, Deng T and Gao J: Tumorspheres derived from HCC cells are enriched with cancer stem cell-like cells and present high chemoresistance dependent on the Akt pathway. Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Cancer Agents) 2015; 15(6): 755-763.
77. Fraser M, Bai T and Tsang BK: Akt promotes cisplatin resistance in human ovarian cancer cells through inhibition of p53 phosphorylation and nuclear function. International Journal of Cancer 2008; 122(3): 534-546.
78. Du K and Montminy M: CREB is a regulatory target for the protein kinase Akt/PKB. Journal of Biological Chemistry 1998; 273(49): 32377-32379.
79. Franke TF, Kaplan DR, Cantley LC and Toker A: Direct regulation of the Akt proto-oncogene product by phosphatidylinositol-3, 4-bisphosphate. Science 1997; 275(5300): 665-668.
80. Siegenthaler JA and Miller MW: Generation of Cajal-Retziusneurons in mouse forebrain is regulated by transforming growth factor β-Fox signaling pathways. Developmental Biology 2008; 313(1): 35-46.
81. Zhu J, Blenis J and Yuan J: Activation of PI3K/Akt and MAPK pathways regulates Myc-mediated transcription by phosphorylating and promoting the degradation of Mad1. Proceedings of the National Academy of Sciences 2008; 105(18): 6584-6589.
82. Wilkens L, Jaggi R, Hammer C, Inderbitzin D, Giger O and von Neuhoff N: The homeobox gene HLXB9 is upregulated in a morphological subset of poorly differentiated hepatocellular carcinoma. Virchows Archiv 2011; 458(6): 697-708.
83. Waltregny D, Alami Y, Clausse N, Leval JD and Castronovo V: Overexpression of the homeobox gene HOXC8 in human prostate cancer correlates with loss of tumor differentiation. The Prostate 2002; 50(3): 162-169.
84. Grassilli E, Ianzano L, Bonomo S, Missaglia C, Cerrito MG, Giovannoni R and Lavitrano M: GSK3A is redundant with GSK3B in modulating drug resistance and chemotherapy-induced necroptosis. PloS One 2014; 9(7): e100947.
85. Veldhoen M, Hocking RJ, Atkins CJ, Locksley RM and Stockinger B: TGFβ in the context of an inflammatory cytokine milieu supports de novo differentiation of IL-17-producing T cells. Immunity 2006; 24(2): 179-189.
86. Arteaga CL: Inhibition of TGFβ signaling in cancer therapy. Current Opinion in Genetics & Development 2006; 16(1): 30-37.
87. Hetzel M, BachemM, Anders D, Trischler G and Faehling M: Different effects of growth factors on proliferation and matrix production of normal and fibrotic human lung fibroblasts. Lung 2005; 183(4): 225-237.
88. Mattson MP, Barger SW, Furukawa K, Bruce AJ, Wyss-Coray T, Mark RJ and Mucke L: Cellular signaling roles of TGFβ, TNFα and βAPP in brain injury responses and Alzheimer's disease. Brain Research Reviews 1997; 23(1-2): 47-61.
89. Massagué J, Blain SW and Lo RS: TGFβ signaling in growth control, cancer, and heritable disorders. Cell 2000; 103(2): 295-309.
90. Verrecchia F and Mauviel A: Transforming growth factor-β signaling through the Smad Pathway: Role in extra-cellular matrix gene expression and regulation. Journal of Investigative Dermatology, 2002; 118(2): 211-215.
91. Guichard C, Amaddeo G, Imbeaud S, Ladeiro Y, Pelletier L, Maad IB and Clément B: Integrated analysis of somatic mutations and focal copy-number changes identifies key genes and pathways in hepatocellular carcinoma. Nature Genetics 2012; 44(6): 694.
92. Tamai K, Semenov M, Kato Y, Spokony R, Liu C, Katsuyama Y and He X: LDL-receptor-related proteins in Wnt signal transduction. Nature 2000; 407(6803): 530.
93. Tian Q, Feetham MC, Tao WA, He XC, Li L, Aebersold R and Hood L: Proteomic analysis identifies that 14-3-3zeta interacts with ⁄-catenin and facilitates its activation by Akt Proc Natl Acad Sci USA, 2004; 101(0027-8424): 15370-15375.
94. Chen Z, Trotman LC, Shaffer D, Lin HK, Dotan ZA, Niki M and Paolo Pandolfi P: Crucial role of p53-dependent cellular senescence in suppression of Pten-deficient tumorigenesis. Nature 2005; 436(7051): 725-730.
95. Di Cristofano A, Pesce B, Cordon-Cardo C and Pandolfi PP: Pten is essential for embryonic development and tumour suppression. Nat. Genetics 1998; 19(4): 348-355.
96. Altomare DA and Testa JR: Perturbations of the AKT signaling pathway in human cancer. Oncogene 2005; 24(50): 7455-7464.

97. Gillis AJ, Schuller AP and Skordalakes E: Structure of the Triboliumcastaneum telomerase catalytic subunit TERT. Nature 2008; 455(7213): 633.
98. Ricchetti M and Buc H: Telomerase activity of reverse transcriptase. Science 1997; 277(5328): 883-887.
99. Blackburn EH: Switching and signaling at the telomere. Cell 2001; 106(6): 661-673.
100. Ozturk M, Li Y and Tergaonkar V: Current insights to regulation and role of telomerase in human diseases. Antioxidants 2017; 6(1): 17.
101. Harris CC: Structure and function of the p53 tumor suppressor gene: clues for rational cancer therapeutic strategies. J Natl Cancer Inst 1996; 88(20): 1442-1455.
102. Zhang X, Miao X, Guo Y, Tan W, Zhou Y, Sun T and Lin D: Genetic polymorphisms in cell cycle regulatory genes MDM2 and TP53 are associated with susceptibility to lung cancer. Human Mutation 2006; 27(1): 110-117.
103. Counter CM, Avilion AA, Lefeuvrel CE, Stewart NG, Greider CW, Harley CB and Bacchettil S: Telomere shortening associated with chromosome instability is arrested in immortal cells which express telomerase activity. The EMBO Journal 1992; 1(1): 921-1929.
104. Pezzuto F, Izzo F, Buonaguro L, Annunziata C, Tatangelo F, Botti G and Tornesello ML: Tumor specific mutations in TERT promoter and CTNNB1 gene in hepatitis B and hepatitis C related hepatocellular carcinoma. Oncotarget 2016; 7(34): 54253-54262.
105. Ferrara N, Gerber HP and LeCouter J: The biology of VEGF and its receptors. Nature Medicine 2003; 9(6): 669.
106. Mfouo-Tynga I and Abrahamse H: Cell death pathways and phthalocyanine as an efficient agent for photodynamic cancer therapy. International Journal of Molecular Sciences 2015; 16(5): 10228-10241.
107. Toyofuku T, Yabuki M, Kamei J, Kamei M, Makino N, Kumanogoh A and Hori M: Semaphorin-4A, an activator for T-cell-mediated immunity, suppresses angiogenesis via Plexin-D1. The EMBO Journal 2007; 26(5): 1373-1384.
108. Umbas R, Schalken JA, Aalders TW, Carter BS, Karthaus HF, Schaafsma HK and Isaacs WB: Expression of the cellular adhesion molecule E-cadherin is reduced or absent in high-grade prostate cancer. Cancer Research 1992; 52(18): 5104-5109.
109. Kolligs FT, Bommer G and Göke B: Wnt/beta-catenin/tcf signaling: a critical pathway in gastrointestinal tumorigenesis. Digestion 2002; 66(3): 131-144.
110. Ishiguro H, Wakasugi T, Terashita Y, Sakamoto N, Tanaka T, Mizoguchi K and Takeyama H: Decreased expression of CDH1 or CTNNB1 affects poor prognosis of patients with esophageal cancer. World Journal of Surgical Oncology 2016; 14(1): 240.
111. Engelman JA: Targeting PI3K signaling in cancer: opportunities, challenges and limitations. Nature Reviews Cancer 2009; 9(8): 550.
112. Hazan RB and Norton L: The epidermal growth factor receptor modulates the interaction of E-cadherin with the actin cytoskeleton. Journal of Biological Chemistry 1998; 273(15): 9078-9084.
113. Hu T and Li C: Convergence between Wnt-β-catenin and EGFR signaling in cancer. Molecular Cancer 2010; 9(1): 236.
114. Hasson CJ, Caldwell GE and Van Emmerik REA: NIH Public Access. Motor Control 2009; 27(4): 590-609.
115. Lague MN, Paquet M, Fan HY, Kaartinen MJ, Chu S, Jamin SP and Boerboom D: Synergistic effects of Pten loss and WNT/CTNNB1 signaling pathway activation in ovarian granulosa cell tumor development and progression. Carcinogenesis 2008; 29(11): 2062-2072.
116. Hazan AD, Smith SD, Jones RL, Whittle W, Lye SJ and Dunk CE: Vascular-leukocyte interactions mechanisms of human decidual spiral artery remodeling *in-vitro*. The American Journal of Pathology 2010; 177(2): 1017-1030.
117. Chen TC, Lin KT, Chen C, Lee S, Lee P, Liu W and Huang CF: Using an in-situ proximity ligation assay to systematically profile endogenous protein-protein interactions in a pathway network. J Proteome Res 2014; 13(12): 5339-5346.
118. Kenny HA, Kaur S, Coussens LM and Lengyel E: The initial steps of ovarian cancer cell metastasis are mediated by MMP-2 cleavage of vitronectin and fibronectin. The Journal of Clinical Investigation 2008; 118(4): 1367-1379.
119. Cherdyntseva NV, Gervas PA, Litvyakov NV, Stakcheeva MN, Ponomaryeva AA, Dobrodeev AY and Choinzonov EL: Age-related function of tumor suppressor gene TP53: contribution to cancer risk and progression. Exp Oncol 2010; 32(3): 205-208
120. Yamane K, Katayama E and Tsuruo T: The BRCT regions of tumor suppressor BRCA1 and of XRCC1 show DNA end binding activity with a multimerizing feature. Biochemical and Biophysical Research Communications 2000; 279(2): 678-684.
121. Rodrigues MS, Machado CA, Pagnoncelli D, Avvad E, PaixãoJC and Gallo CVde M: TP53 and XRCC1 polymorphisms and breast cancer prognosis: a case-case study. Clinics (São Paulo, Brazil) 2011; 66(6): 1097-100.
122. Saikia BJ, Phukan RK, Sharma SK, Sekhon SK and Mahanta J: Interaction of XRCC1 and XPD gene polymorphisms with lifestyle and environmental factors regarding susceptibility to lung cancer in a high incidence population in North East India. Asian Pacific Journal of Cancer Prevention 2014; 15(5): 1993-1999.
123. Kawasaki T, Nosho K, Ohnishi M, Suemoto Y, Kirkner GJ, Dehari R and Ogino S: Correlation of beta-catenin localization with cyclooxygenase-2 expression and CpG island methylator phenotype (CIMP) in colorectal cancer. Neoplasia (New York, N.Y.) 2007; 9(7): 569-77.
124. Kim I, Kwak H, Lee HK, Hyun S and Jeong S: β-Catenin recognizes a specific RNA motif in the cyclooxygenase-2 mRNA 3'-UTR and interacts with HuR in colon cancer cells. Nucleic Acids Res 2012; 40(14): 6863-72.
125. Datan E, Roy SG, Germain G, Zali N, Mclean JE, Golshan G and Zakeri Z: Dengue-induced autophagy, virus replication and protection from cell death require ER stress (PERK) pathway activation. Cell Death and Disease 2016; 7(3): e2127.
126. Ali M, Devkota S, Roh JI, Lee J and LeeHW: Telomerase reverse transcriptase induces basal and amino acid starvation-induced autophagy through mTORC1. Biochemical and Biophysical Research Communications 2016; 478(3): 1198-1204.
127. Cairey-Remonnay S, Humbey O, Mougin C, Algros MP, Mauny F, Kanitakis J and Aubin F: TP53 Polymorphism of Exon 4 at Codon 72 in cutaneous squamous cell carcinoma and benign epithelial lesions of renal transplant recipients and immunocompetent individuals: lack of correlation with Human Papillomavirus Status1. Journal of Investigative Dermatology 2002; 118(6): 1026-1031.
128. De Moraes E, Dar NA, Gallo CVDM and Hainaut P: Cross-talks between cyclooxygenase-2 and tumor suppressor protein p53: Balancing life and death during inflammatory stress and carcinogenesis. International Journal of Cancer 2007; 121(5): 929-937.
129. Serraino M and Thompson LU: The effect of flaxseed supplementation on the initiation and promotional stages

of mammary tumorigenesis. Nutrition and Cancer 1992; 17(2): 153-159.
130. Vogelstein B and Kinzler KW: Cancer genes and the pathways they control. Nat. Medicine 2004; 10(8): 789.
131. Xue C, Plieth D, Venkov C, Xu C and Neilson EG: The gatekeeper effect of epithelial-mesenchymal transition regulates the frequency of breast cancer metastasis. Cancer Research 2003; 63(12): 3386-3394.
132. Jones PA and Baylin SB: The epigenomics of cancer. Cell 2007; 128(4): 683-692.
133. Fønnebø V, Grimsgaard S, Walach H, Ritenbaugh C, Norheim AJ, MacPherson H and Boon H: Researching complementary and alternative treatments–the gatekeepers are not at home. BMC Medical Research Methodology 2007; 7(1): 7.
134. Strausberg RL, Simpson AJ and Wooster R: Sequence-based cancer genomics: progress, lessons and opportunities. Nat Rev Genet 2003; 4: 409-418.
135. Vogelstein B and Kinzler KW: Cancer genes and the pathways they control. Nat Medicine 2004; 10(8): 789.
136. Loeb LA, Loeb KR and Anderson JP: Multiple mutations and cancer. Proc Natl Acad Sci, USA 2003; 100: 776-81.
137. Nowell PC: Tumor progression: a brief historical perspective. Semin Cancer Biol 2002; 12: 261-266.
138. Rajagopalan H, Nowak MA, Vogelstein B and Lengauer C: The significance of unstable chromosomes in colorectal cancer. Nat Rev Cancer 2003; 3: 695-701.
139. Sieber OM, Heinimann K and Tomlinson IP: Genomic instability-the engine of tumorigenesis? Nat Rev Cancer 2003; 3: 701-708.
140. Knudson AG: Mutation and cancer: statistical study of retinoblastoma. Proceedings of the National Academy of Sciences 1971; 68(4): 820-823.
141. Wang TL: Prevalence of somatic alterations in the colorectal cancer cell genome. Proc Natl Acad Sci, USA 2002; 99: 3076-3080.
142. Lengauer C, Kinzler KW and Vogelstein B: Genetic instabilities in human cancers. Nature 1998; 396: 643-49.
143. Duesberg P and Li R: Multistep carcinogenesis: a chain reaction of aneuploidizations. Cell Cycle 2003; 2: 202-10.
144. Mitelman F: Recurrent chromosome aberrations in cancer. Mutat Res 2000; 462: 247-253.
145. Albertson DG and Pinkel D: Genomic microarrays in human genetic disease and cancer. Hum Mol Genet 2003; 12 (spec. no. 2): R145-R152.
146. Shiloh Y and Kastan MB: ATM: genome stability, neuronal development, and cancer cross paths. Adv Cancer Res 2001; 83: 209-254.
147. Scully R and Livingston DM: In search of the tumor-suppressor functions of BRCA1 and BRCA2. Nature 2000; 408: 429-432.
148. Maser RS and De Pinho RA: Connecting chromosomes, crisis, and cancer. Science 2002; 297: 565-569.
149. Pihan G and Doxsey SJ: Mutations and aneuploidy: co-conspirators in cancer? Cancer Cell 2003; 4: 89-94.
150. Rajagopalan H: Inactivation of hCDC4 can cause chromosomal instability. Nature 2004; 428: 77-81.
151. Shay JW and Roninson IB: Hallmarks of senescence in carcinogenesis and cancer therapy. Oncogene 2004; 23: 2919-2933.
152. Shlien A and Malkin D: Copy number variations and cancer. Genome Medicine 2009; 1(6): 62.
153. Chambers AF, Groom AC and MacDonald IC: Dissemination and growth of cancer cells in metastatic sites. Nat Rev Cancer 2002; 2: 563-572.
154. Fidler IJ: Critical determinants of metastasis. Semin. Cancer Biol 2002; 12: 89-89.
155. Houle D, Morikawa B and Lynch M: Comparing mutational variabilities. Genetics 1996; 143(3): 1467-83.
156. Nygren P and Larsson R: Overview of the clinical efficacy of investigational anticancer drugs. J Intern Med 2003; 253: 46-75.
157. Shih LY: Heterogeneous patterns of FLT3 Asp (835) mutations in relapsed de novo acute myeloid leukemia: a comparative analysis of 120 paired diagnostic and relapse bone marrow samples. Clin Can Res 2004; 10: 1326-32.
158. Schottenfeld D and Fraumeni Jr JF: Cancer epidemiology and prevention. Oxford University Press, Edition 1st, 2006.
159. Kinzler KW Vogelstein B: Lessons from hereditary colon cancer. Cell 1996; 87: 159-170.
160. Weissleder R andNtziachristos V: Shedding light onto live molecular targets. Nat Med 2003; 9: 123-128.
161. Sidransky D: Emerging molecular markers of cancer. Nat Rev Cancer 2002; 2: 210-219.

How to cite this article:
Ul-Hasnain MJ, Anwar T, Afzal B, Malik HMT and Abbas SH: Gene pathways in cancer: beginning, ending and the actors of the story. Int J Life Sci & Rev 2018; 4(3): 35-47. doi: 10.13040/IJPSR.0975-8232.IJLSR.4(3).35-47.