Neoplasia from Genetic Point of View

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Received: 23 Dec. 2012; Accepted: 24 Jul. 2013

Abstract- Cancer is a genetic-epigenetic based disease which contains a complex of alterations that cause irreversible transformation of cells with a new anarchic behavior. Tumor suppressor inactivation and/or oncogene activation will lead to tumorigenesis. Based on the genetic alteration in germ or somatic cells, the affected person will have a different fate of cancer incidence or inheritable cancer susceptibility syndrome. Knowing the mechanism of molecular and cytogenetic alterations in cancer will give an advantage in finding more practical approaches to cancer management. In this review, the cancer genetics is discussed from different aspects.

Acta Medica Iranica, 2013; 51(10): 663-674.

Keywords Cancer; Cytogenetics; Epigenetics; Genetics; Oncogenes; Tumor suppressors

Cancer as a genetic disease

Etiology of cancer is always based on genetic alterations (1). For any cell to transform to a neoplasia with no return, several defects will have to take place in the cell genetic map which can lead to new immortal cells with a new pathophysiological behavior (2). Some alterations cannot do anything by themselves. This means that they will make cells susceptible to cancer (3). In such cases, other risk factors will increase the chance of the disease. The transmission pattern of such alterations to the next generations is usually autosomal dominant. So some other alterations are triggering somatic cells into the point of no return (2). That is why, different aspects of cancer genetics is reviewed in this article.

Cancer as a combined genetic alteration

During carcinogenesis many alterations happen inside the cells, thus causing transformation and leading to tumorigenesis. Cells in different steps acquire unusual characteristics which finally change into cancer (2). There are many theories to explain this phenomenon, such as microenvironment (4). Even during the clinical course of the cancer, new unusual characters such as angiogenesis, movement and epithelial to mesenchymal transition which leads to metastasis will be acquired by the cancer cells (4). Some are triggered by stimulants from outside the cells such as stroma, while some others are from inside the cells (5).

Oncogenes versus tumor suppressors

There are two main variants of cancer genes. The first type includes genes that definitely influence tumor formation and are called oncogenes (6). The second type adversely affects tumor growth and are called tumor-suppressor genes (7). Both types of genes employ their influences on tumor growth through their ability in controlling proliferation or apoptosis. In normal cells, oncogenes acquire mutations in cancer cells, which usually lead to relieving the control and enhance gene products activity (6). This occurs in a single allele of the oncogene and acts in a dominant manner. In this case, proto-oncogenes alter to oncogenes. The difference between proto-oncogene and oncogene is based on the activity of the protein which is produced by the gene. A proto-oncogene has a capability of cell transformation in case of genetic damage, while oncogene has the ability of transformation by itself (8). There are different types of proto-oncogenes, listed in table 1. In contrast, the function of tumor-suppressor genes is lost in cancer. They have a recessive characteristic which means both alleles must be inactivated for a cell to completely lose the function of a tumor-suppressor gene (7). This is mentioned by the two-hit hypothesis (9). Some well-known tumor suppressors including p53 (10), retinoblastoma susceptibility gene (RB) (11), Wilms' tumor (WT1) (12), neurofibromatosis type-1 (NF1) (13), familial adenomatosis polyposis coli (APC or FAP) (14) and those identified through loss of heterozygosity such as in colorectal carcinomas (called DCC for deleted in colon carcinoma) (15) have been cited in table 2.

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Table 1. Classification of proto-oncogenes.

Growth Factors
The c-Sis gene encodes the PDGF B chain.
The int-2 gene encodes an FGF-related growth factor.
The KGF (also called Hst) gene also encodes an FGF-related growth factor and was identified in gastric carcinoma and Kaposi's sarcoma cells.
Receptor Tyrosine Kinases
The Flg (*flag*) gene (named because it has homology to the Fms [*fims*] gene, hence fms-like gene) encodes a form of the FGF receptor.
The c-Fms (*fims*) gene encodes the colony stimulating factor-1 (CSF-1) receptor.
The Neu (*new*) gene was identified as an EGF receptor-related gene in an ethylnitrosourea-induced neuroblastoma.
The Trk (*track*) gene encodes the NGF receptor-like proteins. The first Trk gene was found in a pancreatic cancer. There are TrkA, TrkB and TrkC
The Met gene encodes the hepatocyte growth factor(HGF)/scatter factor (9) receptor.
The c-Kit gene encodes the mast cell growth factor receptor.
Membrane Associated Non-Receptor Tyrosine Kinases
The v-src gene was the first identified oncogene.
The c-Src gene is the archetypal protein tyrosine kinase.
The Lck gene was isolated from a T cell tumor line (LYSTRA cell kinase) and has been shown to be associated with the CD4 and CD8 antigens of T cells.
G-Protein Coupled Receptors
The Mas gene was identified in a mammary carcinoma and has been shown to be the angiotensin receptor.
Membrane Associated G-Proteins
There are three different homologs of the c-Ras gene, each of which was identified in a different type of tumor cell. The Ras gene is one of the most frequently disrupted genes in colorectal carcinomas.
Serine/Threonine Kinases
The Raf gene is involved in the signaling pathway of most RTKs. It is likely responsible for threonine phosphorylation of MAP kinase following receptor activation.
Nuclear DNA-Binding/Transcription Factors
The Myc gene was originally identified in the avian myelocytomatosis virus. A disrupted human c-Myc gene has been found to be involved in numerous hematopoietic neoplasias. Disruption of c-Myc has been shown to be the result of retroviral integration and transduction as well as chromosomal rearrangements.
The Fos gene was identified in the feline osteosarcoma virus.
The protein interacts with a second proto-oncogenic protein, Jun to form a transcriptional regulatory complex.

Viruses and cancer

Tumor viruses have two distinct types. Viruses with DNA genomes (*e.g*. papilloma) and with RNA genomes (called retroviruses) (16). RNA tumors are usually seen in animals such as avian, mice and cats and are rare in humans. In humans, T-cell leukemia viruses (HTLVs) and human immunodeficiency virus (HIV) are well known cancer related viruses (17).

In retroviral infection, the RNA genome will convert into DNA by reverse transcriptase enzyme. The converted DNA will then be integrated into the cell genome. The integrated genome will be copied as the cell divides. The genome contains a powerful promoter region called long terminal repeat (LTR) which promotes the transcription of viral DNA and production of new virus particles (18).

The integration into the cell genome is usually random. In occasional cases, if the genome integrates in a proto-oncogene, the LTR can induce the higher gene activity, which means transduction. If the gene has a critical role in cell cycle and growth, it will be imbalanced and leads to uncontrollable growth causing neoplasia (18). Cell transformation mediated by virus DNA can also be caused by proteins encoded for virus called Tumor antigen or T-antigen (19).

Germ cells versus somatic alterations

The vast majority of the mutations that contribute to cancer formation are somatic mutations. This means that they occur in the DNA of a somatic cell, a cell that has a full set of chromosomes but is not used in the creation of the next generation of offspring. Such mutations are

almost always in critical genes which have an important role in growth control. They can lead to uncontrollable cell growth (20). Since such mutations take place in the tumor area, they cannot be detected in other cells like blood in case of solid tumors while there is another type of mutation occurring in germ lines. Such alterations are inheritable mutations and increase the risk of cancer (3) or some polymorphic change related to cancer (21-24). Some of the well-known genes and related syndromes are listed in table 3.

Table 2. Some well- known tumor suppressor genes.

Name	Locus	Functions	Association in Tumors
TP53	17p13.1	Activating DNA repair proteins when DNA has sustained damage. Inducing growth arrest in G1/S Initiate apoptosis, if DNA damage proves to be irreparable.	Adrenal cortical carcinoma Breast cancer Choroid plexus papilloma Colorectal cancer Hepatocellular carcinoma Li-Fraumeni syndrome Li-Fraumeni-like syndrome Nasopharyngeal carcinoma Osteosarcoma Pancreatic cancer
Retinoblastoma susceptibility gene (RB)	13q14.2	Preventing the cell from replicating damaged DNA by preventing its progression along the cell cycle through G1 (first gap phase) into S (synthesis phase) by binding to E2F	Bladder cancer, somatic Osteosarcoma, somatic Retinoblastoma Retinoblastoma, trilateral Small cell cancer of the lung, somatic
Wilms' tumors (WT1)	11p13	Essential role in the normal development of the urogenital system, and it is mutated in a subset of patients with Wilms' tumor.	Denys-Drash syndrome Frasier syndrome Meacham syndrome Mesothelioma, somatic Nephrotic syndrome, type 4 Wilms' tumor, type 1
neurofibromatosis type-1 (NF1)	17q11.2	Negative regulator of the Ras oncogene signal transduction pathway. It stimulates the GTPase activity of Ras. It shows greater affinity for RAS p21 protein activator 1, but lower specific activity	Leukemia, juvenile myelomonocytic Melanoma, desmoplastic neurotrophic Neurofibromatosis, familial spinal Neurofibromatosis, type 1 Neurofibromatosis-Noonan syndrome Watson syndrome
familial adenomatosis polyposis coli (APC or FAP)	5q22.2	Builds a complex with glycogen synthase kinase 3-beta (GSK-3β) and axin then able to bind β-catenins in the cytoplasm, which with the help of casein kinase 1 (CK1), GSK-3β is able to phosphorylate β-catenin followed by ubiquitination and degradation by cellular proteosomes and prevents it from translocating into the nucleus, where it acts as a transcription factor for proliferation genes.	Adenoma, periampullary, somatic Adenomatous polyposis coli Brain tumor-polyposis syndrome 2 Colorectal cancer, somatic Desmoid disease, hereditary Gardner syndrome Gastric cancer, somatic Hepatoblastoma, somatic
Deleted in Colon Carcinoma (DCC)	18q21.2	When not bound to netrin-1, an intracellular domain of DCC is cleaved by a caspase, and induces apoptosis in a caspase-9-dependent pathway.	Colorectal cancer Mirror movements, congenital

Table 3. Major genes in cancer syndromes.

Name	Locus	Syndrome
APC: Adenomatous polyposis coli	5q22.2	Gardner syndrome, Brain tumor-polyposis syndrome, Familial Adenomatous Polyposis, Attenuated Adenomatous Polyposis Coli
ATM: Ataxia–telangiectasia mutated	11q22.3	Ataxia-telangiectasia, B-cell non-Hodgkin lymphoma (somatic), Lymphoma (mantle cell), T-cell prolymphocytic leukemia (sporadic), Breast cancer (susceptibility)
BAX: BCL2-associated X	19q13.33	Colorectal cancer, T-cell acute lymphoblastic leukemia
BMPR1A: Bone morphogenetic protein receptor type 1A	10q23.2	Juvenile polyposis syndrome (infantile form), Polyposis syndrome (hereditary mixed2), Polyposis (juvenile intestinal)
BRCA1: Breast-cancer gene 1	17q21.31	Breast-ovarian cancer (familial), Pancreatic cancer (susceptibility)
BRCA2: Breast-cancer gene 2	13q13.1	Fanconi anemia (complementation group D1), Pancreatic cancer, Prostate cancer, Wilms' tumor, Breast cancer (male susceptibility), Breast-ovarian cancer (familial), Glioblastoma, Medulloblastoma, Pre-B-cell acute lymphoblastic leukemia
BRIP1: BRCA1-interacting protein C-terminal helicase 1	17q23.2	Breast cancer (early-onset), Fanconi anemia (complementation group J)
CASP8: Caspase 8	2q33.1	Hepatocellular carcinoma (somatic), Immunodeficiency due to CASP8 deficiency, Breast cancer (protective), Lung cancer (protective)
CDH1: E-cadherin	16q22.1	Endometrial carcinoma (somatic), Gastric cancer (familial diffuse, with or without cleft lip and/or palate), Ovarian carcinoma (somatic), Breast cancer (lobular), Prostate cancer (susceptibility)
CHEK2: Cell-cycle–checkpoint kinase	22q12.1	Li-Fraumeni syndrome, Osteosarcoma (somatic), Breast and colorectal cancer (susceptibility), Breast cancer (susceptibility), Prostate cancer (familial, susceptibility)
CHRNA3: Cholinergic receptor nicotinic alpha 3	15q25.1	Lung cancer (susceptibility)
CHRNA5: Cholinergic receptor nicotinic alpha 5	15q25.1	Lung cancer (susceptibility)
CHRNB4: Cholinergic receptor nicotinic beta 4	15q25.1	Lung cancer (susceptibility)
FGFR2: Fibroblast growth factor receptor 2	10q26.13	Antley-Bixler syndrome without genital anomalies or disordered steroidogenesis, Apert syndrome, Beare-Stevenson cutis gyrata syndrome, Bent bone dysplasia syndrome, Craniofacial-skeletal-dermatologic dysplasia, Craniosynostosis (nonspecific), Crouzon syndrome, Gastric cancer (somatic), Jackson-Weiss syndrome, LADD syndrome, Pfeiffer syndrome, Saethre-Chotzen syndrome, Scaphocephaly and Axenfeld-Rieger anomaly, Scaphocephaly, maxillary retrusion, and mental retardation
LSP1: Lymphocyte-specific protein 1	11p15.5	Breast Cancer (susceptibility)
MAP3K1: Mitogen-activated protein kinase kinase kinase 1	5q11.2	Familial Breast Cancer, 46XY sex reversal 6

Molecular versus cytogenetic alterations

Cytogenetic changes

In 1956, Tjio and Levan confirmed the correct number of human chromosomes as 46 and established their karyotypic constitution in somatic cells (25). The important points in karyotype are mentioned in table 4. Within a few years, the first meaningful chromosomal changes in human cancer were reported in leukemias (26). Cytogenetic techniques require the presence of dividing cells (preferably in the metaphase stage) for the visualization of chromosomes which means that fresh specimens are necessary. Although uncultured marrow

often contains sufficient dividing cells for cytogenetic studies, short-term culture allows for more efficient analysis (27).

The cytogenetic confirmation in hematologic conditions has become very critical for clinicians in the most cases of leukemias and lymphomas. If tumor is used instead of cultured cells for cytogenetic studies, FISH, PCR, M-FISH, or microarray approaches can be used after therapy to evaluate genetic changes (28). Several types of alterations have been characterized in dominantly acting oncogenes, whose protein products exhibit altered functions and serve to accelerate cell proliferation.

Rearrangements are a common source of activating mutations. Reciprocal translocations represent the most common chromosomal abnormality in leukemias and lymphomas (29). Among them, t(9;22)(q34.1;q11.2), [Philadelphia chromosome] have been well characterized (30). Detection of abnormalities in leukemia is not only useful for diagnostic and treatment purposes, e.g. the t(15;17) (q24;q21) in acute promyelocytic leukemia (31), but also for prognostic risk assessment, such as the t(8;21)(q22;q22) in acute myeloid leukemia (AML). Other critical alterations such as TAL1 gene in T-cell acute lymphoblastic leukemia (T-ALL) (32), translocation t(11;22)(q24;q12) in Ewing sarcoma (EWS) (33) and other soft tissues and bone tumors also exist.

Molecular alterations

Neoplasm is a family of diseases that involves uncontrolled cell division and tissue invasiveness (metastasis). Unregulated cell proliferation and metastasis are caused by mutations in the genes (DNA) of proteins involved in the regulation of the cell cycle. Cancers result from a progressive series of gene mutations that characteristically include two classes of tasks: (a) promotion of cell proliferation and (b) inactivation of cell cycle suppression (34).

From alterations in proto-oncogenes that promote cell proliferation and become oncogenes to alterations in tumor suppressor genes which lead to the loss of heterozygosity and epithelial-mesenchymal transition (35), *i.e.* a molecular orchestration which leads to metastasis, all happen at the molecular level. Oncogenes produce excessive levels of growth promoting proteins (34). Tumor suppressor gene products typified by p53 are frequently transcription factors that suppress mitosis and cell growth to allow for DNA repair. More than half of all cancers involve altered p53 genes (36). Other suppressor genes include Rb (retinoblastoma family), APC (adenomatous polyposis coli), SMAD4, TP53, p16/CDKN2A and BRCA (breast cancer susceptibility protein) types 1 and 2 (37,38).

Cancer stem cells or stem cells to cancer

In the early 1990s, clinical observations and genetic studies of a variety of cancers led to the hypothesis that six genetic mutations were required to convert a normal somatic cell into a cancer cell (39,40). These six mutations included (a) independence for proliferation stimulants, (b) unresponsive to growth arrest signals, (c) outflow of apoptosis, (d) unlimited ability to replicate, (e) continuous angiogenesis, and (f) tissue invasion and metastasis. However, not all cells in a given tissue are created equally in terms of their stage of development and their potential for proliferation and/or differentiation (41).

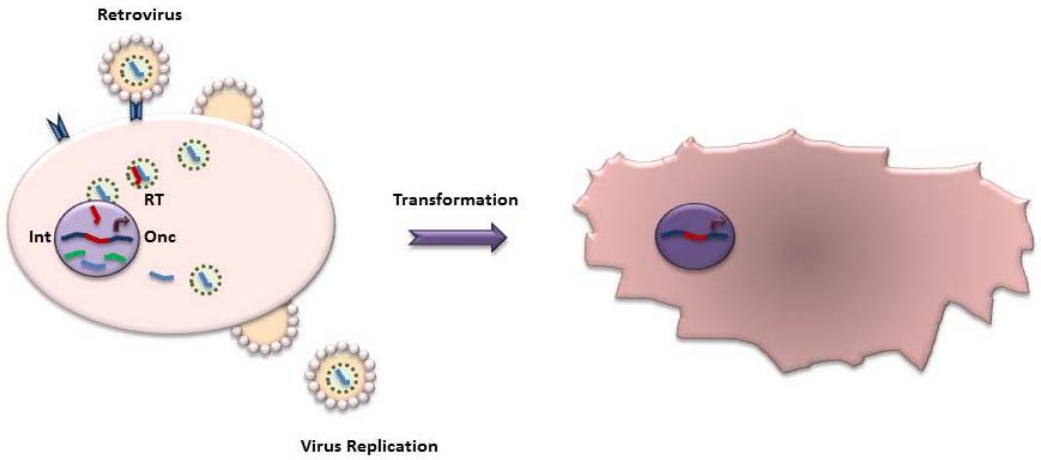

Figure 1. Retrovirus binds to the cell and after fusion the virus will be transcribed to DNA by reverse transcription (RT). The virus DNA will be integrated into the cell genome as random integration followed by RNA transcription and virus replication. In case of random integration beside an oncogene (Onc), cell will transform to neoplastic.

Table 3. Major genes in cancer syndromes (Continue)

Name	Locus	Syndrome
MLH1: MutL homolog 1	3p22.2	Colorectal cancer (hereditary nonpolyposistype 2), Mismatch repair cancer syndrome, Muir-Torre syndrome
MSH2: MutS homolog 2	2p21	Colorectal cancer (hereditary nonpolyposistype 1), Mismatch repair cancer syndrome, Muir-Torre syndrome
MSH6: MutS homolog 6	2p16.3	Colorectal cancer (hereditary nonpolyposistype 5), Endometrial cancer (familial), Mismatch repair cancer syndrome
MSMB: Microseminoprotein, beta	10q11.23	Prostate cancer (hereditary)
MUTYH: MutY homolog	1p34.1	Adenomas (multiple colorectal), Colorectal adenomatous polyposis (autosomal recessive with pilomatricomas), Gastric cancer (somatic)
PALB2: Partner and localizer of BRCA2	16p12.2	Fanconi anemia (complementation group N), Breast cancer(susceptibility), Pancreatic cancer (susceptibility)
PMS2: Postmeiotic segregation 2	7p22.1	Colorectal cancer (hereditary nonpolyposis type 4), Mismatch repair cancer syndrome
PTEN: Phosphatase and tensin homologue	10q23.31	Bannayan-Riley-Ruvalcaba syndrome, Cowden disease, Endometrial carcinoma (somatic), Lhermitte-Duclos syndrome, Macrocephaly/autism syndrome, Malignant melanoma (somatic), PTEN hamartoma tumor syndrome, Squamous cell carcinoma (head and neck, somatic), Thyroid carcinoma (follicular, somatic), VATER association with macrocephaly and ventriculomegaly, Glioma (susceptibility), Meningioma, Prostate cancer (somatic)
STK11: Serine-threonine protein kinase 11	19p13.3	Melanoma (malignant sporadic), Pancreatic cancer (sporadic), Peutz-Jeghers syndrome, Testicular tumor (sporadic)
TP53: Tumor protein p53	17p13.1	Adrenal cortical carcinoma, Breast cancer, Choroid plexus papilloma, Colorectal cancer, Hepatocellular carcinoma, Li-Fraumeni syndrome, Li-Fraumeni-like syndrome, Nasopharyngeal carcinoma, Osteosarcoma, Pancreatic cancer
VHL : von Hippel–Lindau	3p25.3	Erythrocytosis (familial), Hemangioblastoma (cerebellar somatic), Pheochromocytoma, Renal cell carcinoma (somatic), von Hippel-Lindau syndrome
RET: Rearranged during transfection protooncogene	10q11.21	Central hypoventilation syndrome (congenital), Medullary thyroid carcinoma, Multiple endocrine neoplasia IIA, Multiple endocrine neoplasia IIB, Pheochromocytoma, Renal agenesis, Hirschsprung disease (susceptibility)
CDKN2A: Cyclin-dependent kinase inhibitor 2A	9p21.3	Melanoma and neural system tumor syndrome, Orolaryngeal cancer (multiple), Pancreatic cancer/melanoma syndrome, Melanoma (cutaneous malignant)

Stem cells sit at the top of the developmental pyramid, having the ability to self-renew and give rise to all the cell lineages in conforming tissues. Stem cells divide to produce two daughter cells. One daughter remains a stem cell (self-renewal). The other daughter becomes a progenitor cell that undergoes expansion and further differentiates into mature cells. Stem cells have the utmost potential for proliferation and elongated life span compared to their posterity and therefore have a greater occasion to accumulate genetic mutations (42).

Table 4. Important points should be investigated in karyotyping.

1) Differences in chromosome size
2) Differences in the location of the centromere
3) Differences in the basic number of chromosomes
4) The difference in the number and status of microsatellites
5) Differences in the degree and distribution of the heterochromatic region.

Table 5. Common methods in cancer genetics.

Type of Method	Definition
Molecular	
Allele-specific PCR	Finding difference between the two alleles of the point sequence
Methylation-specific PCR	Analyzing DNA methylation in some area, especially in the promoter region
Nested PCR	Elevating the sensitivity used in replication the most wanted portion
Multiplex-PCR	Multiple amplification of DNA from different parts
Quantitative PCR (Real Time PCR)	Monitoring PCR product copy numbers
Reverse Transcription PCR	Transcribing RNA to complementary DNA which called cDNA (complementary DNA)
MLPA (Multiplex Ligation Dependent Probe Amplification)	Ability to amplify various loci by one pair of primer
DNA Sequencing	Sequencing of DNA molecules by labeled nucleotides amplification of DNA
Micro-array	Assembling thousands of the oligonucleotide DNA (sequence-specific DNA) which is called as Probe (or reporter)
Cytogenetic methods	
Fluorescence in situ hybridization (FISH)	Identifying the presence or absence of specific DNA sequences on chromosomes
Chromogenic in situ hybridization (CISH)	using conventional staining, helping to monitor increases the amount of gene activity, chromosomal translocation and the number of chromosomes
Karyotype	Cells culture initially, then, paused in mitosis by using compounds such as colchicine. Subsequently, chromosomes spread on slides, stained and examined under a microscope. Images of chromosomes arranged and placed side by side (Karyogram)
G Banding	Most popular form which is staining by Giemsa. Heterochromatic dark lines or bright areas represent regions of nucleotides AT. GC nucleotides are filled with euchromatic indicator areas.
R Banding	Color appearance is in contrast with G Banding technique.
C Banding	Giemsa is connected to the heterochromatin component and cause centromere staining.
Q Banding	Using fluorescence and it appears similar to G Banding.
T Banding	Using for the telomeres observation.
Silver Nitrate Staining	Using for proteins associated with the nucleolus components staining.

The understanding that the adult body harbors small numbers of stem cells offered an alternative possibility for the origin of cancer. Perhaps only one or two mutations, such as self-sufficiency in growth or insensitivity to antigrowth signals, are needed for stem cells to initiate tumorigenesis rather than six mutations, a rare event in any type of cell. Within established tumors, a great majority of the cancer cells cannot sustain the lesion nor establish it elsewhere in the body. Only a few cells within the tumor, *i.e.* the cancer stem cells, are tumorigenic and possess the metastatic phenotype (42). Now the question is which comes first? Stem cells which turn into cancer stem cells due to accumulated mutations or cancer cells turn into stem cells by mutation (43)? Answering this question is difficult. Still there are many evidences to confirm that stem cells have critical roles in cancer cells' behavior especially during chemotherapy resistance (44).

Genetics and epigenetics

Epigenetics refers to heritable changes in gene expression that occur without alteration in DNA sequence. There are two main epigenetic mechanisms: (a) DNA methylation and (b) covalent modification of histones. Apparently, RNA is closely involved in the gene expression.

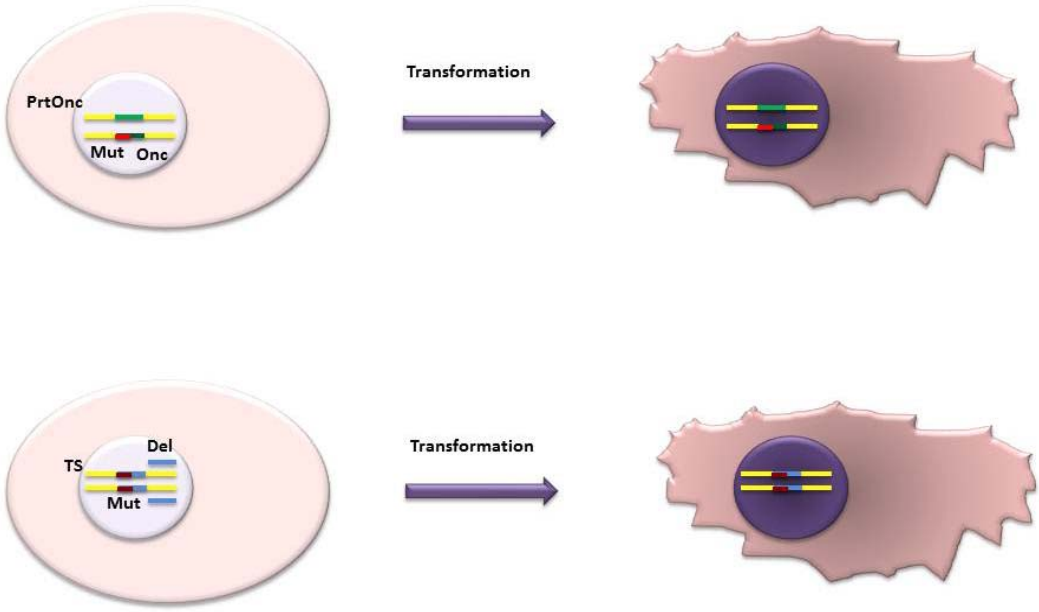

Figure 2. Mutation (Mut) in proto-oncogenes (prtOnc) causes oncogene (Onc) activity and cell transformation which usually occurs in a single allele (dominant manner) while in tumor suppressor (TS) mechanism of neoplasia alterations (such as mutation [Mut] or deletion [Del]) arises in both alleles.

DNA methylation in humans happens more or less completely at CpG dinucleotide and most CpG sequences in the genome are methylated. DNA methylation is catalyzed by a family of DNA methyltransferase enzymes (DNMTs) (45). An excess of covalent post-translational modifications of the histone tails are well-known. The best characterized of these are acetylation, methylation and phosphorylation (46,47). Epigenetic changes occur without alteration in the DNA sequence (48). Thus it is possible, for example, that a DNA mutation leads to cellular transformation, but induced changes in the epigenome of the transformed cell enhances the probability that it will be capable of metastasizing (49).

For instance, studies have demonstrated that sequential gene promoter methylation takes place during HPV-induced carcinogenesis in cervical cancer (50). DNA methylation was the first epigenetic alteration to be observed in cancer cells (51). A number of factors can influence the DNA methylation levels of a cell without requiring a change in genomic DNA sequence including:

1) Aging, in which in certain tissues there is a general tendency for the genome to become hypomethylated whereas certain CpG islands become hypermethylated (52).

2) Diet with nutrition supplies the methyl groups for DNA (and histone) methylation via the folate and methionine pathways (53).

3) Environment and agents such as arsenic and cadmium can have profound effects on DNA methylation. Arsenic causes hypomethylation of the *ras* gene whereas cadmium induces global hypomethylation by inactivating DNMT1 (54).

The histone N-terminal tails are critical in helping to maintain chromatin stability and are subject to numerous modifications which include:

1) Acetylation: Histone acetylation tends to open up chromatin structure. Accordingly, histone acetyltransferases (HATs) tend to be transcriptional activators whereas histone deacetylases (HDACs) tend to be repressors. Many HAT genes are altered in some way in a variety of cancers (46,47).

2) Methylation: All lysine methyltransferases that target histone N-terminal tails contain a so-called SET domain. This domain possesses lysine methyltransferase activity and numerous SET domain-containing proteins are implicated in cancer (55,56).

3) Phosphorylation: H3S10 and H3S28 are phosphorylated at mitosis - a crucial part of the cell cycle; here misregulation is often associated with cancers. Indeed, the Aurora kinases that perform this H3 phosphorylation are implicated in cancer (46,47).

RNA can also be considered as an epigenetic factor involved in chromatin regulation. The RNA interference (RNAi) pathway is also related to chromatin structure;

disturbance of the RNAi mechanism modules distresses the formation of heterochromatin. Micro RNAs affect the expression of genes linked to the cell cycle (*e.g.* down-regulation of E2F1) and expression of miRNAs is altered in cancer cells (57). Moreover, miRNA profiling has shown to be a very valuable assistance to categorizing different cancer types (57,58).

Genetics as a practical approach

Laboratory methods could be classified as molecular and cytogenetics. Molecular methods are mostly by PCR techniques which are designed based on what is happening for DNA replication inside the cell (59-61). In 1993 the inventor of this method, *i.e*. Kary Mullis, won the chemistry noble prize (62). In this process one or more copies of DNA sequences amplify from thousands to millions of copies of the same DNA. The process was based on a thermal cycle including several heating and cooling cycles for the opening sequence of DNA molecules and DNA replication. In general, compounds of this process is composed of a pair of primer complementary strands of DNA (Forward or Reverse), a special buffer, bivalent cations such as magnesium and manganese, nucleic acid molecules, 3 phosphate (dNTP) and Taq polymerase enzyme to the transcription used. This enzyme is derived from a bacterium called Thermus Aqualiticus (59-61). There are different variations of molecular methods (63-71) which have been mentioned in table 2. Concerning the cytogenetic techniques, there are three popular methods such as FISH (72) and CISH (73) and the most popular form which is karyotype (74-78) (Table 4).

Future of genetic manipulations

It is obvious that science of genetics has had an accelerated rate of improvement in the recent decades. Cellular and molecular bases of diseases especially in cancer have come to spotlight. Although there are many unanswered questions, recent results show a promising future for cancer genetics. Gene therapy may not have its practical way in cancer, but there are many hopeful results in various studies showing modified methods in gene delivery and cell-based gene therapy which can lead to more successful results and enlighten the future of practical genetics in cancer (79).

Acknowledgments

The authors would like to thank Seyed Muhammed Hussein Mousavinasab for his sincere cooperation in editing this work.

Condensation

This is a review article discussed about cancer genetics. It is accepted that cancer is a genetic-epigenetic disease with many different alterations which cause cancer or cancer susceptibility.

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