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Review Article

A PIVOTAL ROLE OF INSULIN LIKE GROWTH FACTOR IN MALIGNANT NEOPLASM

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ABSTRACT

Epigenetics, this is a new frontier in biology, helpful to find the involvement of altered genetic functions in different disease, to understand the proper reason and also to find a new therapy. Cancer which is medically known as malignant neoplasm occurs when problem of gene of a cell prevents the control of functional property. Along with the involvement of several genes IGF-II (insulin-like growth factor 2) plays a great role in the development of cancer. This insulin like growth factor -2 over expression may result from the loss of genomic imprinting in IGF-II, loss of function of transcriptional repressor. The present work was aimed to reviewing the proper order of information regarding the role of IGF-II gene in cancer especially colorectal and how IGF-II family especially IGF-II itself involved in cancer inherited in nature and the process of control the expression either by DNA methylation or by imprinting IGF-II itself or in relation with H-19 gene. It was envisaged that this set of review in future prospective will be helpful for the new research scientist in this particular area to know about the involvement of IGF-II in cancer and will open the new direction of work for the development of gene therapy in the treatment of cancer.

Keywords: IGF-II, Inherited cancer, Epigenetic, Imprinting.

INTRODUCTION

Cancers are caused by a series of mutations. Each mutation alters the behavior of the cell. Cancer is fundamentally a disease of failure of regulation of tissue growth. In order for a normal cell to transform into a cancer cell, the genes which regulate cell growth and differentiation must be altered[1]. The affected genes are divided into two broad categories. Gene seems to have 2 major roles in cancer. Some are called oncogenes, which can cause cancer. Others, known as tumor suppressor genes,which stop cancer from developing or growing. Oncogenes are mutated forms of certain normal genes of the cell called proto-oncogenes. Proto-oncogenes are the genes that normally control what kind of cell it is and how often it grows and divides. When a proto-oncogene mutates (changes) into an oncogene, it turns on or activates when it is not supposed to be. When this occurs, the cell can grow out of control, leading to cancer. Tumor suppressor genes are normal genes that slow down cell division, repair DNA mistakes, and tell cells when to die (a process known as apoptosis or programmed cell death). When tumor suppressor genes don't work properly, cells can grow out of control, which can lead to cancer. A tumor suppressor gene is like the brake pedal on a car. It normally keeps the cell from dividing too quickly just as a brake keeps a car from going too fast. When something goes wrong with the gene, such as a mutation, cell division can get out of control[2-3]. An important difference between oncogenes and tumor suppressor genes is that oncogenes result from the activation(turning on) of proto-oncogenes, but tumor suppressor genes cause cancer when they are inactivated (turned off). Even if you were born with healthy genes, some of them can become changed (mutated) over the course of your life. These mutations are known as sporadic or somatic, meaning they are not inherited. Sporadic mutations cause most cases of cancer. These mutations are thought to be caused by things that we are exposed to in our environment, including cigarette smoke, radiation, hormones, and diet. More gene mutations build up as we get older, leading to a higher risk of cancer. When someone has inherited an abnormal copy of a gene, their cells already start out with one mutation. This makes it all the easier (and quicker) for enough mutations to build up for a cell to become a cancer. That is why cancers that are inherited tend to occur earlier in life than cancers of the same type that are not inherited [4].

Genetic changes can occur at different levels and by different mechanisms. The gain or loss of an entire chromosome can occur through errors in mitosis. Most common are mutations, which are changes in the nucleotide sequence of genomic DNA [5]. Large-scale mutations involve the deletion or gain of a portion of a chromosome. Genomic amplification occurs when a cell gains many copies (often 20 or more) of a small chromosomal locus, usually containing one or more oncogenes and adjacent genetic material. Translocation occurs when two separate chromosomal regions become abnormally fused, often at a characteristic location. A well-known example of this is the Philadelphia chromosome, or translocation of chromosomes 9 and 22, which occurs in chronic myelogenous leukemia, and results in production of the BCR-abl fusion protein, an oncogenic tyrosine kinase [6].

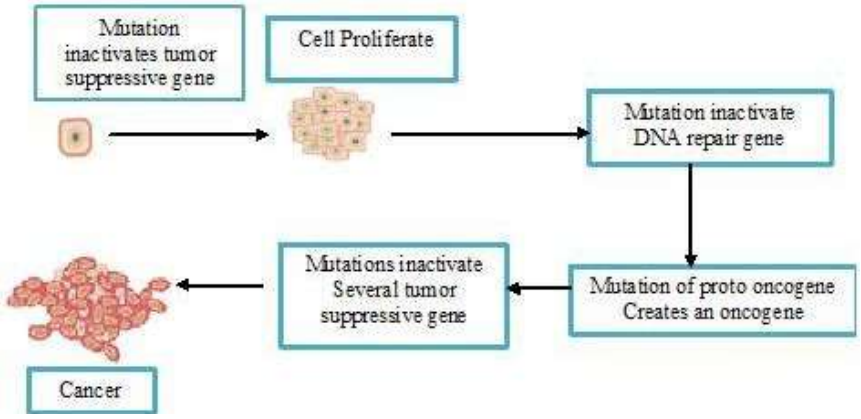

Fig. 1: Steps in the formation of carcinogenesis

Small-scale mutations include point mutations, deletions, and insertions, which may occur in the promoter region of a gene and affect its expression, or may occur in the gene's coding sequence and alter the function or stability of its protein product. Disruption of a single gene may also result from integration of genomic material from a DNA virus or retrovirus, and resulting in the expression of viral oncogenes in the affected cell and its descendants [7-8]. Replication of the enormous amount of data contained within the DNA of living cells will probabilistically result in some errors (mutations). Complex error correction and prevention is built into the process, and safeguards the cell against cancer. If significant error occurs, the damaged cell can "self-destruct" through programmed cell death, termed apoptosis.

If the error control processes fail, then the mutations will survive and be passed along to daughter cells. The goal of gene therapy in cancer is to replace damaged genes with ones that work to address a root cause of cancer: damage to DNA. For example, researchers are trying to replace the damaged gene that signals cells to stop dividing (the p53 gene) with a copy of a working gene. Other gene-based therapies focus on further damaging cancer cell DNA to the point where the cell commits suicide. Gene therapy is a very young field and has not yet resulted in any successful treatments [9]. The steps in carcinogenesis [5] formation shows in figure 1.

IGF-II structure, locations and functions

The official name of this gene is insulin-like growth factor 2 (somatomedin A). IGF-II is the gene's official symbol. In humans, the IGF-II gene is located on chromosome 11p15.5, a region which contains numerous imprinted genes. [10] In mice this homologous region is found at distal chromosome 7. In both organisms, IGF-II is imprinted, with expression resulting favorably from the paternally inherited allele. The protein CTCF is involved in repressing expression of the gene, by binding to the H19 imprinting control region (ICR) along with Differentially-methylated Region-1 (DMR1) and Matrix Attachment Region-3 (MAR3). These three DNA sequences bind to CTCF in a way that limits downstream enhancer access to the IGF-II region. The mechanism in which CTCF binds to these regions is currently unknown, but could include either a direct DNA-CTCF interaction or it could possibly be mediated by other proteins and Fig 1 shows the protein structure of IGF-II [11].

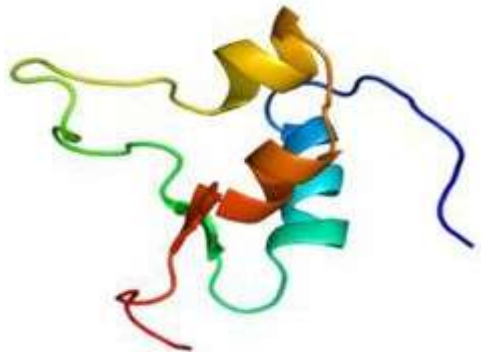

Fig. 2: Structure of the IGF2 protein based on PyMOL **rendering of PDB**

(Source: http://en.wikipedia.org/wiki/Insulin-like_growth_ factor_2**)**

IGF-II exerts its effects by binding to the IGF-1 receptor. IGF-II may also bind to the IGF-II receptor (also called the cation-independent mannose 6-phosphate receptor), which acts as a signaling antagonist; that is to prevent IGF-II responses. [11] The following functions are performed by the gene under study**:**

1. The major role of IGF-II is as a growth promoting hormone during gestation. In the process of Folliculogenesis, IGF-II is created by Theca cells to act in an autocrine manner on the theca cells themselves, and in a paracrine manner on Granulosa cells in the ovary [12-13] .
2. IGF-II promotes granulosa cell proliferation during the follicular phase of the menstrual cycle, acting alongside Follicle Stimulating Hormone (FSH). After ovulation has occurred, IGF-II promotes progesterone secretion during the luteal phase of the menstrual cycle together with Luteinizing Hormone (LH). Thus, IGF-II acts as a Co-hormone together with both FSH and LH. A study at the Mount Sinai School of Medicine found that IGF-II may be linked to memory [14].
3. The IGF-II gene provides instructions for making a protein called insulin-like growth factor 2. This protein plays an essential role in growth and development before birth. Studies suggest that insulin-like growth factor 2 promotes the growth and division (proliferation) of cells in many different tissues. Although the IGF-II gene is highly active during fetal development, it is much less active in the adult body. [15]
4. IGF-II is a part of a cluster of genes on the short (p) arm of chromosome 11 that undergo genomic imprinting. Another gene in this cluster H19 also involved in growth and development. A nearby region of DNA known as imprinting center 1 (ICR1) or the H19 Differentially Methylated Region (H19 DMR) controls the parent-specific genomic imprinting of both the H19 and IGF-II genes. [16]

Cytogenetic Location of IGF-11 is 11p15.5 and molecular Location on chromosome 11 is base pairs 2,150,346 to 2,170,832

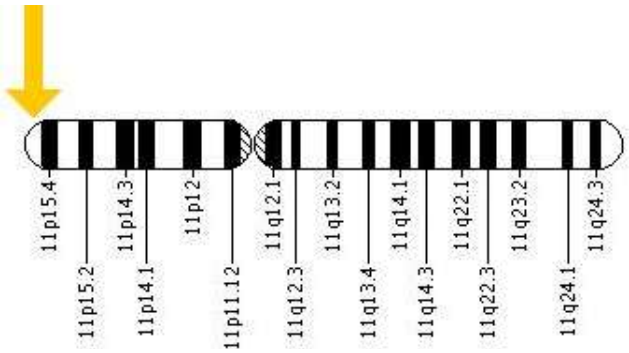

Fig. 3: Cytogenetic Location of IGF-II

(Source: http://ghr.nlm.nih.gov/handbook/howgeneswork/genelocation)

The *IGF-II* gene is located on the short (p) arm of chromosome 11 at position 15.5. More precisely, the *IGF-II* gene is located from base pair 2,150,346 to base pair 2,170,832 on chromosome 11 given [17] in figure 3.

Cancers - associated with the IGF-II gene

Increased activity of the IGF-II gene has been associated with many types of cancer. Normally, the IGF-II gene undergoes genomic imprinting and only the copy inherited from a person's father is active. In some cancers, however, both the paternal and the maternal copies of the gene are active, increasing the amount of insulin-like growth factor 2 that cells can produce. This phenomenon is known as loss of imprinting (LOI) [18]. An increased amount of insulin-like growth factor 2 may stimulate the growth of tumor cells and prevent damaged cells from being destroyed. Loss of imprinting of the IGF-II gene has been identified in several types of cancer known as embryonal tumors. These tumors include a rare form of kidney cancer called Wilms tumor, a cancer of muscle tissue called rhabdomyosarcoma, and a form of liver cancer called hepatoblastoma. Although these tumors commonly occur in people with Beckwith-Wiedemann syndrome, loss of imprinting of the gene has also been seen in people with these tumors who do not have Beckwith-Wiedemann syndrome. Loss of imprinting of the IGF-II gene has also been found in many other types of cancer, including cancer of blood-forming cells (leukemia) and cancers of the breast, prostate, lung, colon, and liver. Researchers suspect that this genetic change may someday be used to help predict a person's risk of developing these forms of cancer [19-20].

IGFs are also over expressed in certain cancers. Animal experiments indicate that over expression of IGF-I increases the likelihood of tumor development in certain tissues. Over expression of IGF-II may result from loss of genomic imprinting in IGF-II, loss of function of a

transcriptional repressor, or change of transcription promoter sites. Cancer cells with a strong tendency to metastasize have higher expression of IGF-II and IGF-IR (IGF-I receptor) than those with a low ability to do so. [21] The strong impact of IGF-II on cancer growth that is observed consistently in laboratory studies and the paucity of clinical and epidemiologic studies that have found an association between circulating IGF-II and cancer risk suggest that IGF-II may exert its action via paracrine rather than endocrine regulation.

The effects of IGFs on cancer cells are mediated through IGF-IR. Eliminating IGF-IR from the cell membrane, blocking the interaction of IGFs with IGF-IR, or interrupting the signal transduction pathway of IGF-IR can abolish the mitogenic action of IGFs on cancer cells IGF-IR also plays a critical role in cell transformation that is induced by tumor-virus proteins and oncogene products. IGF-IR is involved not only in the induction of cell transformation but also in the maintenance of the transformed phenotype IGF-IR is over expressed in certain cancers, and its over expression is associated with aggressive tumors The hybrid receptor that binds both IGF-IR and insulin may also mediate the effect of IGFs on cancer. A recent study indicates that the insulin receptor is involved in mediating the actions of IGF-II on breast cancer [22].

Since IGF-IIR antagonizes the effect of IGF-II, loss of IGF-IIR function is expected in cancer. One study found cancer-related missense mutations in the IGF-IIR gene with resultant disruption of the binding of IGF-IIR to its ligand. Cancer cells that lack the ability to degrade IGF-II have been shown to have a strong growth potency suppressing the expression of IGF-IIR yields the same effect as mutation in the IGF-IIR gene. Re-establishing the function of IGF-IIR in cancer cells that lack IGF-IIR reduces cancer growth and increases apoptosis.

In cancer, IGFBPs (Insulin like growth factor binding proteins) regulate the action of IGFs. In most situations, the binding proteins suppress the mitogenic action of IGFs and promote apoptosis [23]. However, because of the presence of IGFBP proteases, two *in vitro* studies have found that IGFBPs are able to stimulate the growth of cancer cells. Oh et al. found that IGFBP-3 inhibited breast cancer cell growth without interacting with IGFs. Other studies [24] reported that IGFBP-3 could induce apoptosis of breast and prostate cancer cells without the presence of IGFs or IGF-IR. Effects of insulin like growth factors and growth factor1 receptor on normal and cancerous cell and their relationship has been shown [15] schematically in figure no.4

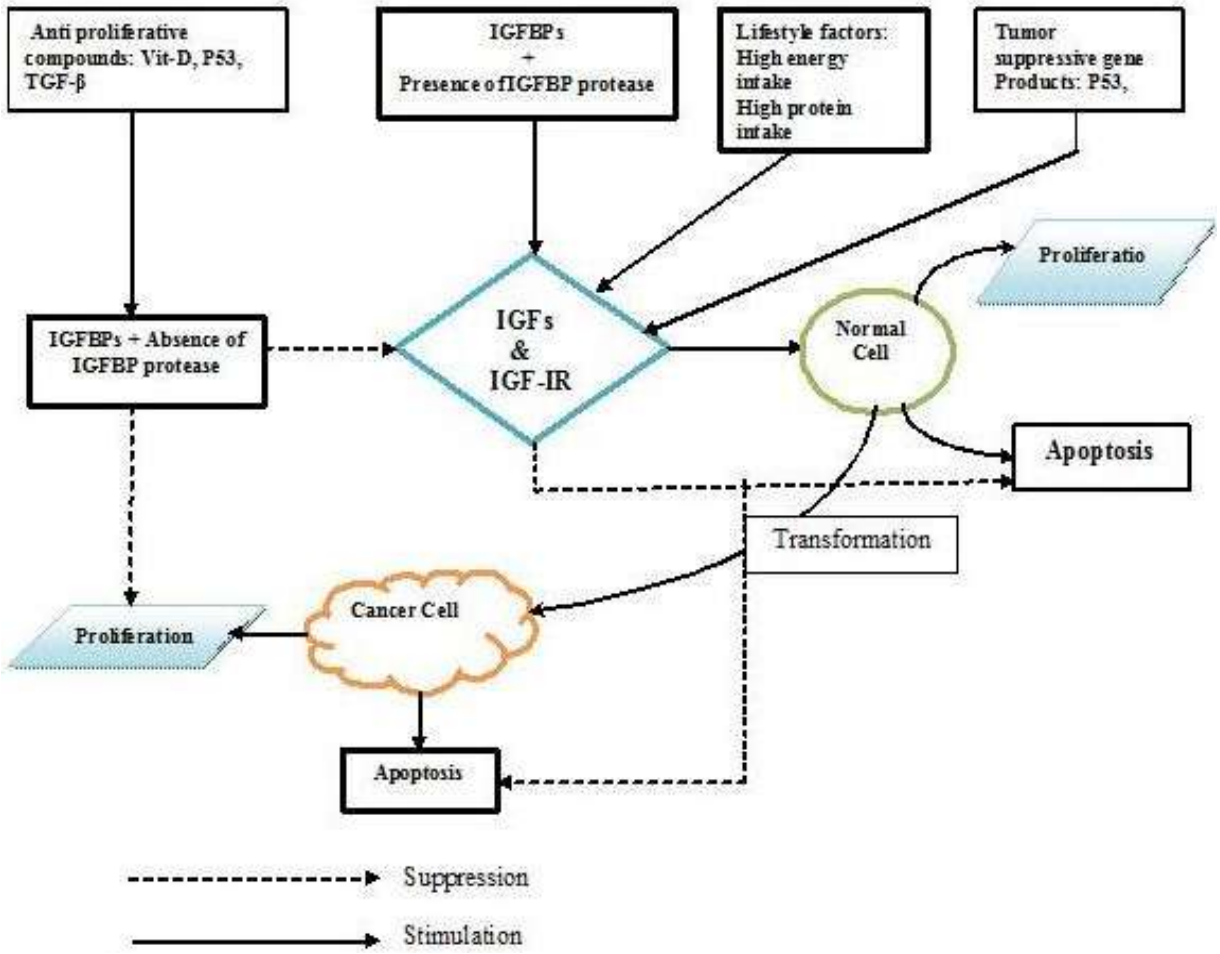

Fig. 4: Effects of insulin like growth factors and growth factor1 receptor on normal and cancerous cell and their relationship in mitigenetic and antiproliferative molecules, tumor suppressor gene products and lifestyle factors. Solid arrow indicates stimulation and dashed arrow indicates suppression. Question marks indicate the effects remains to be determine.

EGF: Epedimal growth factor, GH: Growth Hormone, IGF: Insulin like growth factor, IGFBP: Insulin like growth factor binding protein, IGF-IR and IGR-I receptor.TGF: Transforming growth factor.

Insulin-Like Growth Factor Family and Cancer Development

IGFs play an important role in regulating cell proliferation, differentiation, apoptosis, and transformation [25]. IGFs exert their actions by interacting with a specific receptor on the cell membrane, namely, the IGF-I receptor (IGF-IR), and the interaction is regulated by a group of specific binding proteins. All of these molecules are considered to be members of the IGF family, which includes the polypeptide ligands IGF-I and IGF-II, two types of cell membrane receptors (i.e., IGF-IR and IGF-IIR), and six binding proteins (i.e., IGFBP-1 through IGFBP-6). *H Yu et.al* described the molecular features of insulin like growth factor family given in Table 1. In

addition, a large group of IGFBP proteases hydrolyzes IGFBPs, resulting in the release of bound IGFs that then resume their ability to interact with IGF-IR. Thus, as far as IGF action is concerned, IGFBP proteases may also be regarded as part of the IGF family because they indirectly regulate the action of IGFs [26-27].

IGF-I and IGF-II are single-chain polypeptides. [28-29] The two molecules have 62% homology in their amino acid sequences. The molecules share additional structural similarities, and their structures resemble the structure of proinsulin. The IGF-I gene is located on chromosome 12 and the IGF-II gene is located on chromosome 11, 1.4 kilo bases (kb) downstream from the insulin gene[30]. Table 1 summarizes some features of IGF molecules and of their encoding genes.

The IGF-I gene has two promoter sites, and the IGF-II gene has four promoters, i.e., P1–P4. [31] Multiple transcripts (i.e., messenger RNAs) for both IGFs have been identified. Initiation of transcription at different promoter sites and alternative splicing are believed to be responsible for producing the multiple transcripts. [32-33,-34] The presence of distinct transcripts is usually indicative of diverse responses of cells to different environmental stimuli, and animal studies have suggested that diet and nutrition may induce different patterns of IGF-I transcription. In adult tissues, IGF-II transcription is initiated from the P1 promoter. Transcription from promoters P3 and P4 is often seen in fetal tissues, and increased transcription from these promoter sites has been observed in certain cancer tissues [35-36]. Both IGF-IR and IGF-IIR are glycoproteins are located on the cell membrane. The two receptors, however, differ completely in structure and function.

Binding of IGFs to IGF-IR activates the receptor's tyrosine kinase activity, which triggers a cascade of reactions among a number of molecules involved in the signal transduction path-way. Two distinct signal transduction pathways have been identified for IGF-IR. One pathway activates Ras protein, Raf protein, and mitogen-activated protein kinase, and the other pathway involves phosphoinositol-3-kinase. Other signal transduction pathways that are initiated by IGF-IR may also exist. Activation of IGF-IR by ligand binding is necessary to allow IGF-IR to mediate the actions of IGFs. In addition to mediating the mitogenic and antiapoptotic actions of IGFs, IGF-IR is involved in cell transformation. In vitro experiments have shown that removal of IGF-IR from the cell membrane by eliminating the IGF-IR gene, by suppressing its expression, or by inhibiting its function can abolish cell transformation [37]. IGF-IIR has no tyrosine kinase activity, and it binds only to IGF-II. Since binding of IGF-IIR to IGF-II results in degradation of IGF-II, IGF-IIR acts like an antagonist to IGF-II, reducing its biologic activity. Because of this effect, IGF-IIR has been considered to be a potential tumor suppressor molecule. A unique feature of IGF-IIR may contribute to its ability to act as a scavenger for circulating IGF-II [38-39].

Table 1: Members of the insulin-like growth factor family and their molecular feature *

	Molecular weight, kd	No. of amino acids	Gene location	Gene size, kb	No. of exons
IGF-I	7.7	70	12q22–12q24	100	6
IGF-II	7.5	67	11p15	30	9
IGF-IR	225	−-subunit: 706 $_3$-subunit: 626	15q25–15q26	100	21
IGF-IIR	270	2450	6q25–6q27	140	Unknown
IGFBP-1	25.3	234	7p12–7p14	5.2	4
IGFBP-2	31.4	289	2q31–2q34	32	4
IGFBP-3	28.7	264	7p12-7p14	8.9	5
IGFBP-4	26.0	237	17q12–17q21	12	4
IGFBP-5	28.6	252	2q31–2q24	33	4
IGFBP-6	22.8	216	12q13	4.7	4

***Abbreviations used:** IGF - insulin-like growth factor; IGFBP - insulin-like growth; factor-binding protein; IGF-IR -IGF- I receptor; IGR-IIR - IGF-II receptor; kb - kilobases; kd - kilodaltons. IGF-IR is a tetrameric protein (two and two -subunits).

Interrelationship between IGF-II and H19 gene expression in cancer

Genomic imprinting is surmised to have arisen due to the conflicting interests of maternal and paternal genes within a pregnancy. Within a pregnancy, the father wants the mother to devote as much of her resources as possible towards the growth (benefit) of his offspring. However, within the same pregnancy, the mother wants to conserve as much of her resources as possible towards future births without compromising the health of the children she is currently carrying. H19 contains a Differentially Methylated Region that is also an imprinting control region. This imprinting control region is differentially methylated at its CpGs according to parental inheritance [40]. Usually, the paternal copy of H19 is methylated and silent while the maternal copy is hypomethylated or unmethylated and expressed in the offspring cell. Methylation of the H19 promoter is negatively correlated with H19 expression. As methylation of the promoter reaches 100%, H19 expression from that promoter approaches. At the same time as H19 expression decreases, the expression of IGF-II, a neighboring gene on chromosome 11, increases. Cells treated with Azad, a demethylating agent, grow much slower than cells cultured in the absence of Azad. At the same time, H19 expression increases while IGF-II expression decreases in the presence of Azad. The reduction of IGF-II expression could be a reason for the slower growth of cells treated with Azad [41]. As well, in a mouse bladder carcinoma cell line, where transfection of a human H19 DNA construct results in high expression of H19, the methylation of the H19 promoter reduces H19 expression. The paternal H19 allele, which is silent postnatal, shows increasing methylation of CpGs in its promoter with gestation time in the fetus. It appears conclusive that the H19 gene is epigenetically controlled via methylation, where methylation on or near the vicinity of one allele prevents the expression of that allele. As well, based on the results from Banet *et al.*, it appears that functional H19 imprinting occurs during early placenta development [42]. Increased H19 expression is found in the following cancers: adrenocortical neoplasms, choriocarcinomas, hepatocellular carcinomas, bladder cancers, ovarian serous epithelial cancers, head and neck carcinomas, endometrial cancer, breast cancer, acute T cell leukemia/lymphoma, Wilms' tumor, testicular germ cell cancer, esophageal cancer and lung cancer [43].

Adrenocortical neoplasms

In contrast to most other cancers, adrenocortical neoplasm appears to have decreased expression of H19. To determine a possible cause for the down regulation of H19, Gao *et al.* studied the methylation of 12 CpG sites in the H19 promoter in normal, hyperplasia, adenoma and carcinoma adrenals. They found that in carcinomas, there was more methylation of CpGs than in normal, hyperplasia and adenoma adrenals. Consequently, normal H19 expression was detectable in normal and hyperplasia adrenals, but in carcinomas and surprisingly, adenomas, there was a lower H19 expression that was coupled with detectable (increased) IGF-II expression [44].

Choriocarcinomas

Choriocarcinomas, in contrast to adrenal carcinomas, have up regulated H19 and down regulated IGF-II expression. The up regulated H19 expression, however, came from alleles that were fully methylated. Surgically removed choriocarcinomas from human

patients also exhibited a heavily methylated H19 promoter with enhanced H19 expression. This led researchers Arima *et al.* to suggest that in cases of choriocarcinomas, the H19 promoter was mutated, allowing it to overcome the transcriptional repression of promoter CpG methylation [45].

Hepatocellular carcinoma

In hepatocellular carcinoma, the expression of H19 and IGF-II usually changes from monoallelic to biallelic. In *in vitro* studies, culturing hepatocellular carcinoma cell lines in hypoxic condition up regulated H19 expression. Whether or not the loss of imprinting for the H19 promoter is a characteristic of hepatocellular carcinoma is not known, as some cell lines exhibit loss of imprinting while others did not.

Bladder cancers

Bladder mucosa is one of the tissues that express high levels of H19 RNA prenatally. In bladder cancers, H19 is also up regulated and present in most stages. The presence of H19 RNA was strongest in bladder carcinomas (sampled in situ) that tend to progress rapidly to invasive cancer as well as invasive transitional cell carcinomas [46].

In samples of bladder carcinoma, loss of imprinting at the H19 loci was observed. Verhaugh *et al.* investigated various polymorphisms in the H19 gene and found that some heterozygous SNP polymorphisms, such as rs2839698 TC, were associated with a decreased risk of developing non-muscle invasive bladder cancer as well as bladder cancer overall; however, this association disappeared for homozygotes (CC) [47].

***Endometrial/ovarian* cancer**

In normal endometrial tissue, there is no H19 expression; however, in endometrial cancer, H19 is expressed. The expression level of H19 RNA in the epithelial cells of the endometrium increases as tissue differentiation is lost in endometrial cancer.

In ovarian cancers, 75% of low malignancy tumors and 65% of invasive ovarian carcinomas are H19 RNA positive [48].

Breast cancer

Normal breast tissue does not express H19 RNA, except during puberty and pregnancy in the mammary glands.

However, in breast cancer, 72.5% of the breast adenocarcinomas studied by Adriaenssens *et al.* displayed increased H19 expression when compared to normal breast tissue. Of the tissues with up regulated H19, 92.2% are stromal cells and only 2.9% are cells. Studies by Berteaux *et al.* have also found that the over expression of H19 in breast cancer cells promotes proliferation. The expression of H19 in these cells is also independent of the tumor suppressor protein p53 and the cell cycle marker Ki-67.However, the presence of tumor suppressor protein pRb and transcription factor E2F6 is sufficient to repress H19 expression in breast cancer cells [49].

Genetics, Genomics, and Cancer: The Future Trends

As a new decade unfolds, we are very fortunate to have an increasing number of new interventions available because of the recent tremendous advances in genetics and genomics. While a variety of disorders associated with single gene mutations have been understood for decades, information from sequencing the complete human genome, together with new technologies, has created opportunities in medicine with far reaching implications.

We are constantly building on our understanding of normal and aberrant genetic function and how differences in gene products, or "molecular signatures," can be associated with specific clinical characteristics and diseases. Genomic research is uncovering ways that interactions among genes, one's environment and culture, and other factors can affect disease development and prognosis. Evolving research in this area will continue to inform our assessment of individual risk, selection of therapy, and predictions of outcome. Personalized healthcare is becoming a reality [50].

The application and integration of genetic and genomic knowledge [51] to elicit and analyze family health history in conjunction with other risk factors; identification of patients who may benefit from specific genetic/genomic information or services; referral of at-risk patients and families for genetic/ genomic services as needed; and provision of education, care, and support, utilizing genetic and genomic based information and interventions to improve outcomes. Lea and Calzone highlight the many applications of genetics and genomics to the care of individuals with, or at risk for, specific solid and hematologic malignancies from diagnosis and prognosis (e.g., BRCA1 and BRCA2 mutations), to progression (e.g., micro-RNA expression in hepatocellular carcinoma), to choosing the most appropriate therapy (e.g., breast tumor ERBB2 gene expression to determine eligibility for trastuzumab (Drug information on trastuzumab) [Herceptin], or assessment of KRAS status in colorectal cancer prior to initiating EGFR inhibitor therapy), or monitoring the response to a given agent.

So the knowledge in genetics, genomics, and pharmacogenomics has to offer: risk reduction and prevention; earlier, more accurate diagnosis; better and more effective intervention and treatment; avoidance of expensive, toxic, and unnecessary therapy; an improved survival benefit; and a more satisfying quality of life.

DISCUSSIONS

It is now clear that the genome contains the information in two forms, genetics and epigenetic. The genetic information provides the blue prints for the manufacturing of all the proteins, necessary to create the organism. While the epigenetic information provides additional instruction that how, when and where the genetic information should used. The epigenetic information is not contained within the DNA sequence itself, but can specify the emiotic inheritance of cell fate and gene expression patterns and can then environmental effects into heritable changes in cell phenotype. The major forms of epigenetic modifications in mammalian cells in DNA methylation i.e. Covalent addition of the methyl group to the 5^{th} position of the cytosine within CPG dinucleotides, predominantly located at the promoter region. Recent work has revealed that DNA methylation is an important player in many processes including DNA repair, genome instability and regulation of chromatin structure. The epigenetic inheritance may be mediated by two other processes, aside from DNA methylation, namely histone modification and genomic imprinting. By keeping the interest on the above facts hence the present work by reviewing the proper, order wise information entitled "a pivotal role of insulin like growth factor -2 genes in cancer" was done. Starting from history, basics of cancer and its therapy, involvement of genetic genetic alterations in the development of cancer has been established by giving the stress on IGF-II gene. This information will make easy understanding of how IGF-II gene is associated with the development of different types of cancer and the process of control the expressions, either by DNA methylation or by imprinting of IGF-II itself or along with H19 gene. It was envisaged that this set of review with the future prospective will helpful for the new research scientist in this particular area to know the basics and will open the new direction of work. It must be helpful for the students in different backgrounds to know about this devastating disease.

It was expecting that total collective work by taking this burning disease and its new therapy will be helpful for the society and concluding by expecting with this hope no more die will occur in future in this world with this devastating disease.

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