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Atielogy and Pathophysiology of Neoplastic Growth

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Abstract: Neoplasia is a literal translation of the Greek word "new growth'. Neoplastic cells are said to be transformed because they replicate continuously, heedless and in perfect asynchronism to the regulatory influences that govern normal cell growth. As a result, a fundamental characteristic of neoplasms is the loss of responsiveness to regular growth control resulting from failure of the usual mechanisms that control cellular proliferation and maturation. Moreover, this random growth continues even in the absence of the stimulus. In this study, the cellular, molecular and biochemical mechanisms of carcinogenesis are analysed. This entails a detailed discussion of the cell cycle and its fine regulation together with an explanation of the link between the cell cycle and induction of cancer. Proto-oncogenes and tumor-suppressor genes are also discussed. Finally, the genetic aspect of cancer is tackled.

Key words: Atielogy, neoplastic growth, pathophysiology, neoplasms, asynchronism

INTRODUCTION

Neoplasm, as defined by Rupert Willis, is an abnormal mass of tissue, the growth of which is uncoordinated with that of normal tissues and that persists in the same excessive manner after the cessation of the stimulus which evoked the change (APQUB, 2003).

Neoplastic cells are said to be transformed because they replicate continuously, heedless and in perfect asynchronism to the regulatory influences that govern normal cell growth. As a result, a fundamental characteristic of neoplasms is the loss of responsiveness to regular growth control resulting from failure of the usual mechanisms that control cellular proliferation and maturation. Moreover, this haphazardous growth continues in the absence of the stimulus, contrasting sharply with hyperplasia in which growth cessation ensues on removal of the stimulus involved (Stevens and Lowe, 2000).

THE CELLULAR, MOLECULAR AND BIOCHEMICAL MECHANISMS OF CARCINOGENESIS

As previously alluded to, neoplastic growth is characterized by a state of unregulated cell growth. A neoplasm has nothing to do with an infectious disease induced by a microorganism- it is simply a cell that all of a sudden has been transformed. Therefore, it is crucial to delve into the molecular mechanisms that tune normal cell growth in healthy cells. What governs regular cell proliferation in healthy cells? This is the fundamental dogma which must be answered before proceeding to understand the molecular mechanisms which induce neoplastic growth and enhance its proliferation. This question arises naturally since before proceeding to understand the abnormal, one must know thoroughly the normal.

A cell is an autonomous unit. All the instructions needed to direct its activities are contained within its DNA (Deoxyribonucleic Acid) located in the nucleus. As already stated, cells are continuously dividing into new cells referred to as daughter cells. This is vital to replace the lost cells. The chain of events occurring in eukaryotic cells between one cell division and the next which therefore encompasses DNA replication is referred to as the cell cycle. This is exclusive to eukaryotic organisms.

The eukaryotic cell cycle is divided into various stages and check points with each stage being dominated by a particular event taking place in the cell.

The G_1 phase or first gap phase precedes replication. In this stage, the cell is in the diploid state. Late in the G_1 phase, the commitment to divide is triggered in a still not known way. Synthesis of histones is one of the first signals of incipient DNA replication since division requires doubling of the DNA content which in turn requires new histones for the production of chromatin.

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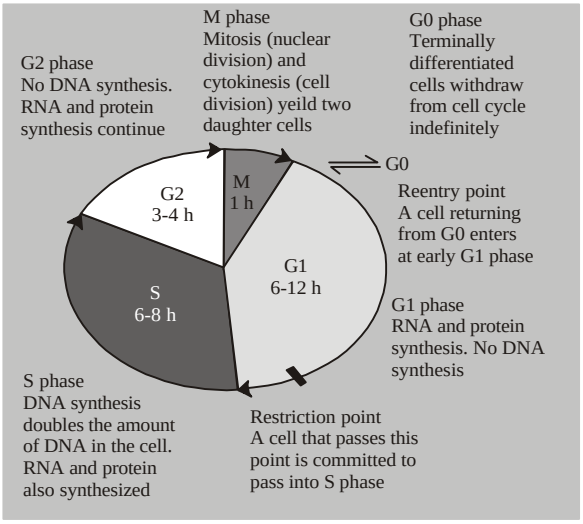

Fig. 1a: The main stages of the cell cycle

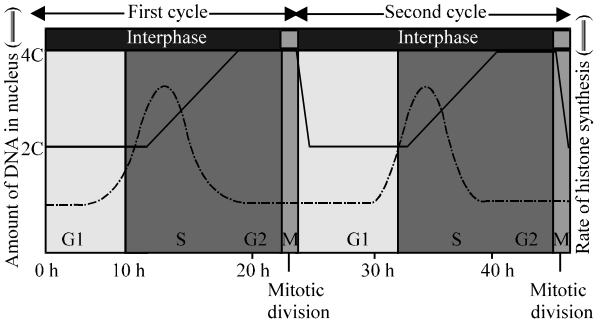

Fig. 1b: Changes in DNA content throughout the various stages of the cell cycle

The cell then enters the S phase or synthesis phase. During this period, replication of the DNA proceeds and the histones and non-histone proteins are deposited on the daughter DNA molecules to produce chromatin. When replication is complete, the cell enters the G_2 or Gap_2 phase. At this stage, the cell has DNA content four times the haploid amount. In most eukaryotic cells, the total time required for G_1, S and G_2 phases will be many hours but this obviously is highly variable.

During this entire period known as interphase, the chromatin is dispersed throughout the nucleus, being actively engaged in transcription. At the end of the G_2 phase, the cell is prepared to start mitotic division and this is known as the M phase which is in turn divided into prophase, metaphase, anaphase and telophase ending in cytokinesis.

Figure 1 (a and b) are two representations of the eukaryotic cell cycle, showing the various phases just mentioned above. Figure 1a shows an overview of the different stages of the cell cycle while Fig. 1b includes some details of what happens at each stage as well as the approximate average duration of the various stages.

In prophase, the chromosomes become condensed and the nuclear envelope breaks down. This is followed by metaphase where the chromosomes come to lie in the equatorial plane and mitotic spindles are clearly evident. During anaphase, the chromatids are pulled to opposite sides of the pole so that each daughter cell possesses one sister chromatid. Telophase is the reverse of prophase where the chromosomes exit their condensed form and become loose again and the nucleolus and nucleus reform. Cytokinesis is produced by invagination of the cell membrane via furrowing yielding two daughter cells.

After passing through mitosis into the G_1 phase, the cell either continues the process, resulting in another cell division or else if it ceases to divide, it enters a quiescent phase known as the G_0 stage. This stage has a variable duration and it may last from hours to days all the way up to the lifetime of the cell. Cells such as neurons which do not divide remain in the G_0 phase.

REGULATION OF THE CELL CYCLE

After understanding what the cell cycle is and its main stages and events taking place in each phase, a crucial question that arises is: How is the cell cycle regulated?

The cell makes two important all-or-none decisions during the cell cycle: the first decision is taken late in the G_1 stage and concerns the entry into the S phase. DNA replication should initiate only when the cell is prepared to progress through the entire cell cycle and it should embark only after any DNA damage sustained during the preceding stages has been thoroughly repaired via DNA repair mechanisms.

The second all-or-none decision regards the entry into mitosis. Mitosis should proceed only after the completion of DNA replication and only if the replicated chromosomes are structurally intact. Once initiated mitosis proceeds through all the stages (Nelson and Cox, 2000).

These two all-or-none decisions define the G_1 checkpoint and the G_2 checkpoint, respectively.

The regulation of the cell cycle depends on the interaction of two basic proteins, namely Cyclin-Dependent Kinases (CDKs) and a group of regulatory proteins called cyclins which orchestrate the metabolic activities of the cell to produce orderly and tightly controlled cell division. As their name implies, cyclin dependent kinases are only active when bound to the respective cyclin. Cyclin concentrations are in turn regulated by synthesis and degradation.

The activity of cyclin dependent kinases during the progression of the cell cycle is regulated by a number of molecular mechanisms.

The first level of regulation involves the association of cyclin dependent kinases with their cyclin partners. The formation of specific CDK-cyclin complexes is tuned by cyclin degradation and synthesis as previously alluded to.

Activation of the CDK-cyclin complex requires phosphorylation of a conserved threonine residue around position 160. Phosphorylation of a different amino acid which is tyrosine will inhibit the cyclin dependent kinase's activity. Dephosphorylation of these tyrosine residues is required in order to switch the cyclin dependent kinases back to their active state.

The activity of cyclin dependent kinases is also controlled by the binding of inhibitory proteins known as CDK Inhibitors (CDKI). Control of these inhibitors thus provides an additional mechanism by which the activity of cyclin dependent kinases is controlled.

Growth factors and cytokines also play a role in regulating the synthesis of cyclins and cyclin dependent kinases. These have the potential to transducer gene induction, proliferation or programmed cell death, that is, apoptosis. Growth factors result ultimately in cell division thru an enzyme cascade that activates MAPK (Mitogen-Activated Protein Kinase) by which transcription factors such as Jun and Fos are phosphorlylated, thus activating the transcription factor E2F, which enhances the production of enzymes crucial for DNA replication as well as activating transcription of cyclin D, cyclin E, CDK2 and CDK4. The role of growth factors is illustrated in Fig. 2.

Mitogenic growth factors are important between the onset of the G_1 phase and a point later in the G_1 phase known as the restriction point beyond which the remaining phases of the cell cycle are not under the influence of extracellular signals and are committed to progress rather than quiesce.

The combined effects of these multiple modes of cyclin dependent kinases regulation are responsible for controlling the course of the cell cycle in response to both the checkpoint controls and to a variety of other extracellular stimuli that influence cell proliferation.

In eukaryotic cells Cdc2 is also known as CDK-1 which together with cyclins A and B control mitosis.

After having discussed the control mechanisms which govern the activity of cyclin dependent kinases, it is worth looking in detail at the structure of these kinases and how this structure enables them to subserve their function.

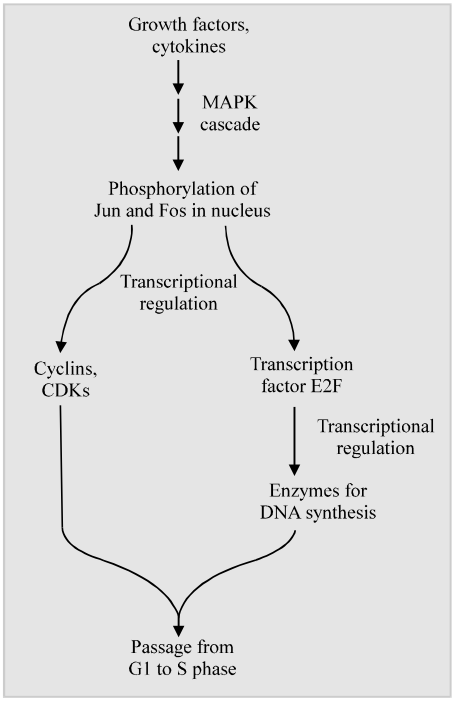

Fig. 2: Regulation of cell division by growth factors (Nelson and Cox, 2000)

CDK-cyclin complexes can be considered as heterodimers with a regulatory subunit, cyclin and a catalytic subunit, Cyclin-Dependent protein Kinase (CDK). In the absence of cyclin, the catalytic subunit is virtually inactive (Wikipedia, 2006). When cyclin binds, the catalytic subunit opens up, a residue essential for catalysis is accessible and the activity of the catalytic subunit increases about 10,000 fold (Nelson and Cox, 2000).

Animal cells have at least ten different cyclins (designated A,B, etc) and at least 8 Cyclin-Dependent Kinases (CDK 1-8) which act in various combinations at different stages throughout the cell cycle. Certain cyclin dependent kinase activities exhibit striking oscillations as is portrayed in a population of animal cells undergoing synchronous cell division. This results from the four major mechanisms regulating cyclin dependent kinase activity namely whether it is phosphorlylated or dephosphorylated; the degradation of the cyclin subunit; phasic synthesis of the respective cyclin dependent kinases and cyclins and the effect of cyclin dependent kinases specific inhibitors.

Each transition in the cell cycle has a unique cyclin-kinase complex as its trigger. For instance, the complex cyclin E-CDK2 activity peaks near the G_1 phase-S phase boundary where the active enzyme triggers synthesis of

enzymes required for DNA synthesis. On the other hand, cyclin A-CDK2 complex is dominant during the S phase and G_2 phase and then dwindles down in the M phase where cyclin B-CDK1 peaks. These oscillations are illustrated in Fig. 3.

There is a feedback loop in which increased cyclin dependent kinase activity turns on cyclin proteolysis. Newly synthesized cyclin activates cyclin dependent kinase by associating with it and this, in turn, activates DBRP (Destruction Box Recognition Protein) by phosphorylating it. Active DBRP then induces prtoteolysis of cyclin. It does this by causing the attachment of ubiquitin molecules to cyclin by the enzyme ubiquitin ligase. Hence, it is the cyclin-CDK complex itself, which via negative feedback, triggers its own inactivation. Lowered cyclin concentrations on the other hand causes cyclin dependent kinase activity to decrease, lowering down the activity of DBRP also drops through slow constant dephosphorylation and inactivation by a DBRP phosphatase. Synthesis of new cyclin molecules helps to restore the cyclin level. This is summarized in Fig. 4.

The next question that stems out is: How does CDK activity control the cell cycle?

Cyclin dependent kinases regulate cell division by phosphorylation of critical proteins.

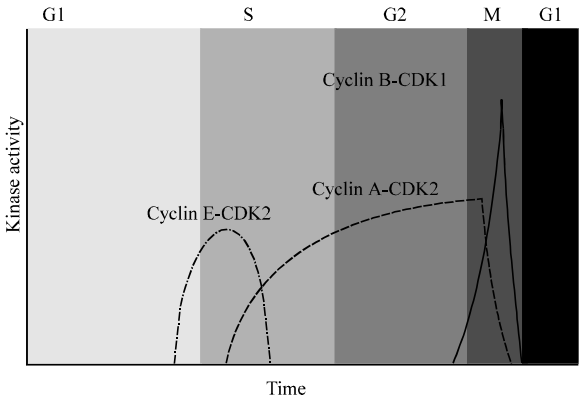

Fig. 3: A unique cyclin-kinase complex is needed for each stage of the cell cycle (Nelson and Cox, 2000)

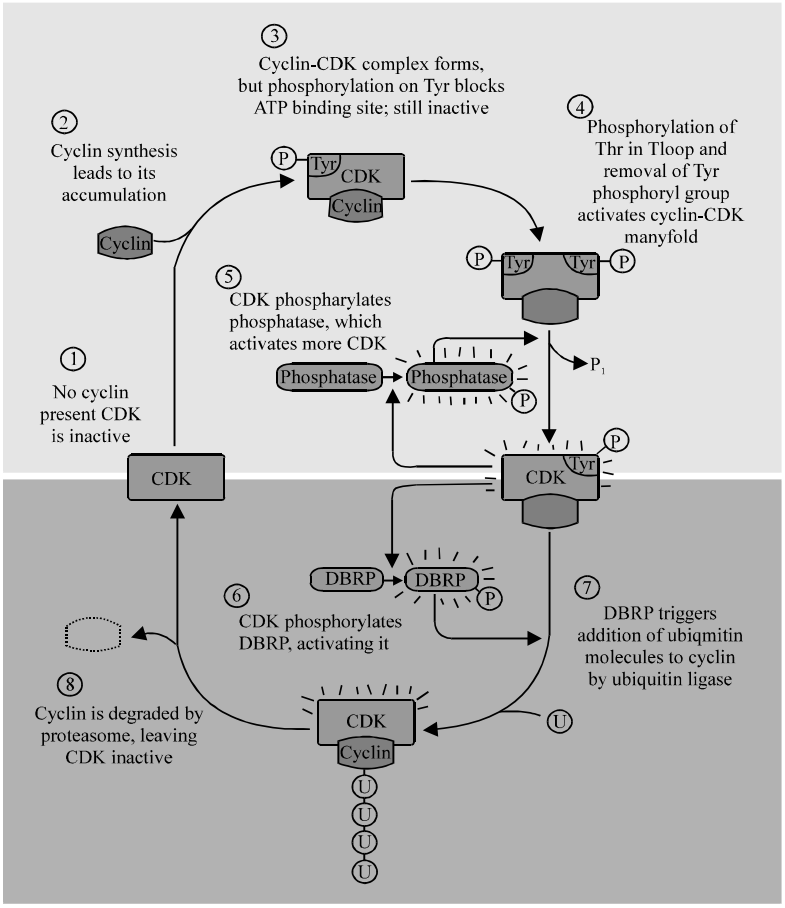

Fig. 4: The feedback loop involved in the regulation of cyclins (Nelson and Cox, 2000)

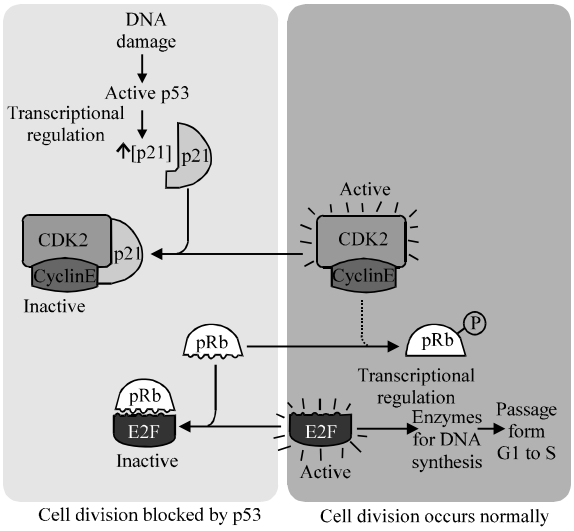

Fig. 5: The role of Retinoblastoma protein (pRb) in the regulation of cell division (Nelson and Cox, 2000)

Phosphorylation, as part of a control mechanism, is reflected in all major physiological mechanisms and keeps on repeating itself as a means by which a variety of proteins and molecules are activated.

The targets of cyclin dependent kinases are many and include laminin, myosin and Retinoblastoma protein (pRb) amongst others.

Laminin is vital for the cytoarchitecture and in fact highly organized meshworks of intermediate filaments composed of laminin are a requisite for the structure of the nuclear envelope. It follows then, that breakdown of the nuclear envelope in the prophase stage of mitosis is due to depolymerisation of laminin filaments. It is partly due to the phosphorlyation of laminin by a particular cyclin dependent kinase that this disorganization of laminin takes place.

During cytokinesis, the cell membrane undergoes furrowing. This requires an ATP-driven actomyosin contractile machinery. Once cell division has taken place, it is the cyclin dependent kinase that phosphorylates a small regulatory subunit of myosin, separating myosin from actin filaments and thus inactivating the contractile machinery.

Retinoblastoma protein (pRb) functions in all cell types as a surveillance system which controls cell division in response to various stimuli. When in the unphosphorylated state, pRb binds to the transcription factor E2F and in this state, E2F fails to trigger transcription of the enzymes required for the synthesis of DNA and thus the cell cycle remains in the G1 stage without embarking on to the S phase. The complex cyclin E-CDK2 phosphorylates pRb and so cell division can go on since the blocking effect is eliminated. Figure 5 summarises the role of pRb.

THE LINK BETWEEN THE CELL CYCLE AND CANCER

Both the cell cycle and cancer are extremely interesting scientific fields which only recently have had their molecular mechanisms unraveled. However, the overlap that exists between cancer and cell cycle is even much more alluring than the above 2 aspects of science independently. Even at first glance, the link between cell cycle and cancer is obvious. As described above, the cell cycle is the guard which controls normal cell division and proliferation while in cancer it is exactly this that has become abnormal. In fact, it is said that normal growth control and malignancy are two faces of the same coin (Lodish *et al*., 2000).

Incidentally, also quite recently, the field of molecular genetics is rapidly gaining ground as well. This aspect of science together with the molecular mechanisms of the cell cycle have merged together to shed light on the atielogy of cancer and its pathophysiology. In fact, genetic alterations play a significant role in the alteration of the normal cell cycle mechanisms and therefore cause a cell to undergo malignant change. Two main types of genetic alterations have been identified, involving either mutations which cause activation of function or else mutations which cause loss of function of certain genes.

GAIN-OF-FUNCTION MUTATIONS: THE PROTO-ONCOGENES

The conversion of proto-oncogenes into oncogenes portrays an example of a gain-of- function mutation. The products of these proto-oncogenes are crucial for cellular signaling and the ordered progression through the cell cycle and cell division. Their vital roles are reflected in the fact that they have been highly conserved throughout evolution. It follows that if a proto-oncogene undergoes a somatic mutation, cell growth and proliferation become erratic and thus malignant change ensues (Mueller and Young, 2002).

An oncogene codes for a protein which has the capacity to induce unrestrained growth and trigger neoplasia. Although some oncogenes are derived from mutated proto-oncogenes, one must bear in mind that only a small part fall into this category (Lodish *et al*., 2000).

The *ras* gene, for example, is a proto-oncogene that codes for an intracellular signal-transduction protein.

Therefore, when this gene undergoes a mutation and hence become an oncogene, the oncoprotein it produces, leads to abnormal growth (Lodish *et al*., 2000).

The process of activating a proto-oncogene into an oncogene via a gain-of-function mutation involves a number of different mechanisms. Three mechanisms are believed to play a role in this change. These mechanisms involve either point mutations in the proto-oncogene that code for an active protein or duplication of a particular part of DNA resulting in multiple copies of the same gene, leading to increased translation of the protein or else they involve a chromosomal translocation which results in a change in the promoter of the gene resulting in abnormal translation of the gene. As is conveyed through these different mechanisms, oncogenes are either mutated proto-oncogenes or else proto-oncogenes expressed at abnormal levels (Lodish *et al*., 2000; Mueller and Young, 2002).

Contrary to tumor suppressor genes which will be dealt with later on, mutation in only one of the alleles is enough to induce neoplastic growth (Lodish *et al*., 2000).

In 1911 Peyton Rous conducted a series of studies that eventually introduced the novel concept that viruses can induce cancer. The virus he worked with is known as Rous Sarcoma Virus (RSV) and fifty years later in 1966 his concept was acknowledged and he was awarded the Nobel Prize for this discovery (Lodish *et al*., 2000). As the era of molecular biology set in, it was shown that RSV is a retrovirus. This means that like HIV (Human Immunodeficiency Virus) it has RNA (Ribonucleic Acid) as its genetic material and undergoes reverse transcription using the enzyme reverse transcriptase to transform RNA into DNA. It was found that oncogenic transforming viruses such as RSV possess the *v-src* gene apart from other normal commonly found genes such as *gag*, *pol* and *env* which encode for structural proteins for the core antigens, reverse transcriptase and glycoproteins in the envelope, respectively (Mueller and Young, 2002). It was further unravelled that it is only the *v-src* gene that is responsible for neoplasia and not the other ones. It causes abnormally high levels of v-src protein which results in aberrant phosphorylation of several proteins. At this point the *v-src* gene was identified as an oncogene (Lodish *et al*., 2000).

As already alluded to, because of the possession of the *v-src* oncogene, RSV is able to trigger neoplasia and it does so within days. However, most carcinogenic retroviruses take a much longer time span to cause neoplastic growth. This stems from the fact that these slow acting or long latency retrovirus do not have an oncogene which directly enhances neoplasia. Hence, they cause cancer via a different mechanism involving the translation of the *c-myc* gene which is important for the production of proteins concerned in the control of the cell cycle. The proviral DNA can act as a promoter or an enhancer of *c-myc* transcription resulting in a perfectly normal expressed protein but produced at much higher concentrations which accounts for the induction of neoplasia. Moreover, the proviral DNA prevents downregulation of the protein and thus cells instead of differentiating, keep on proliferating. These slow-acting viruses are much more common than the fast-acting viruses which possess an oncogene (Lodish *et al*., 2000).

Apart from retroviruses, DNA-containing viruses are also potential triggers of neoplasia. A classical example is the Human Papilloma Virus (HPV) which causes warts and benign tumors in the epithelium.

LOSS-OF-FUNCTION MUTATIONS: TUMOR SUPPRESSOR GENES

The second type of mutations responsible for induction of neoplastic growth are the loss-of-function mutations as opposed to those mentioned above which involve a gain of function. These classes of mutations involve what are known as tumor-suppressor genes. Tumor suppressor genes code for proteins that normally restrain unlimited cell division. Therefore, it is quite easily conceivable that abnormalities in this gene result in abnormal growth (Lodish *et al*., 2000; Mueller and Young, 2002).

Tumor suppressor genes code for 5 main classes of proteins, namely intracellular proteins such as the p16 cyclin-kinase inhibitor, p53, p21 and Retinoblastoma protein (pRb); receptors for secreted hormones such as TDGF $ (Tumor Derived Growth Factor $) that are crucial for preventing excess cell growth; check point control proteins that instantly stop the cell cycle if they detect any abnormalities; proteins that enhance programmed cell death, that is apoptosis and also enzymes active in DNA repair mechanisms (Lodish *et al*., 2000).

As can be seen tumor suppressor genes are crucial for ensuring normal proliferation of cells and thus it is inevitable that defects in the proteins they code for, lead to neoplasia.

Unregulated growth due to defective tumor suppressor genes is genetically recessive. This means that unlike the *v-src* gene, tumors in this case, form only if both chromosomes of a pair are defective. An individual who inherits one correct copy and another effected copy will not be diseased, but has a higher risk of developing cancer since only one hit is needed to acquire 2 mutant alleles. Thus if any one of the 10^{12} somatic cells subsequently acquires a mutation in the good copy, a

tumor will then grow from that doubly mutated cell. This highlights the fact that although one copy of a mutated gene does not directly give rise to neoplasia, indirectly it has the potential to do so in the long run, as it greatly increases the risk of abnormal growths (Mueller and Young, 2002). Nondisjunction and mitotic recombination may play a role in producing a cell with two mutated gene copies which originally had only one mutated gene. This event is known as Loss of Heterozygosity (Lodish *et al*., 2000).

A classic case of loss of Heterozygosity which leads to abnormal function of pRB (retinoblastoma protein) is retinoblastoma which is a highly malignant childhood cancer of the retinal cells in the eye. Retinoblastoma can occur either sporadically without being inherited or else it is said to be familial, that is, inherited. Non-hereditary cases occur in individuals who are born with two normal alleles for retinoblastoma protein but have acquired mutations in both the alleles. In these cases, the disease affects one eye and is very rare. In hereditary cases, which are often bilateral, the individual inherits one defective allele and so has a high predisposition to developing retinoblastoma. When he acquires a mutation in the only normal allele, then, he develops the disease. Thus retinoblastoma is an autosomal dominant trait (Lodish *et al*., 2000; Mueller and Young, 2002).

This genetic predisposition to the premature onset of cancer is also highlighted in breast cancer which has been linked to the tumor-suppressor gene known as BRCA1 where woman who inherit one mutant BRCA1 allele run a 60% risk for developing breast cancer as opposed to normal women having normal BRCA1 in both copies of the genes which have merely a 2% chance of developing breast cancer (Lodish *et al*., 2000).

Another tumor suppressor gene well studied by the help of ‘gene knockout techniques’ apart from the pRb gene is the p53 gene. As with the pRb gene, inheritance of one abnormal copy of the gene predisposes the individual to formation of neoplasia. In fact, in rare cases, these individuals may present with several tumor growths in different tissues; a condition known as Li-Fraumeni syndrome (Mueller and Young, 2002; NCBI, 2006).

The p53 gene is located on chromosome 17 and codes for the p53 protein which is a multimeric protein that enhances the production of a protein called p21 which activates which is a CDK inhibitor. P21 can bind to and inhibit cyclinE-CDK2, thus preventing phosphorylation of pRb. Unphosphorylated pRb binds to E2F and inactivates it, thereby preventing the progression of the G1 phase to the S phase (NCBI, 2006). Mutant p53 leads to inavailability of the p21 to bind to and inhibit cyclinE-CDK2. Thus, pRb remains phosphorylated and no longer inactivates E2F so that cell division is unrestricted. Thus, it naturally follows that p53 is one of the major key proteins involved in tumor formation and proliferation (NCBI, 2006).

Experiments on knockout mice have revealed interesting information. We have been faced with the concept that proteins like p53 not only regulate cell proliferation but also regulate apoptosis which is programmed cell death. This opens doors to new line of thoughts especially when it comes to devising drugs used in chemotherapy. Maybe instead of manufacturing drugs that inhibit or try to keep within control cell division, we should target drugs that enhance apoptosis so that tumor cells are induced to program their own cell death (Collins *et al*., 1997).

THE GENETIC ASPECT OF CANCER

Although not all of the mutations in tumor suppressor genes or proto-oncogenes are inherited, mutations in these genes are commonly seen in cancers that run in families. The inheritance of a mutant allele does not mean that the individual is going to develop cancer but predisposes the particular person to a greater risk than another one who has both of the alleles normal. A typical example is inherited defects in the *APC* (*Adenomatous polyposis coli*) gene that are responsible for Familial Adenomatous Polyposis (FAP), leading to the formation of numerous colon polyps that could eventually become neoplastic (American Cancer Society, 2005; Mueller and Young, 2002).

It must be understood that the majority of colorectal cancers are sporadic and in fact, only 1% of persons diagnosed with colorectal cancer have inherited the defective APC gene. Similarly, a person who has developed numerous polyps in his colon because of this gene, does not necessarily mean, that he will develop cancer because not all polyps undergo malignant change, although the risk is quite high (Mueller and Young, 2002).

The fact some of the cancers run in families and are due to certain defective genes is the rationale behind genetic testing. Genetic testing includes performing several tests to identify whether genes such as BRCA1 are present in the genome and thus advising the individual about the risk of developing cancer.

As can be concluded, cancer stems from a mutation in a part of the DNA of the cell. Researchers studying cancer used to believe that carcinogenesis is caused solely by carcinogens such as cigarette smoke, chemicals or radiations. Others believed that it is an entirely genetic disease. However in the 1970s, as molecular biology paced at a big step, scientists observed that all factors

that in one way or another have the potential to trigger neoplasia, target the cell's DNA and modify it.

Bert Vogelstein, an HHMI (Howard Hughes Medical Institute) investigator at The Johns Hopkins Oncology Center in Baltimore states that cancer, though it has a genetic aspect, differs from most other genetic diseases in two ways. First of all, individuals may inherit defective genes which increase their predisposition to cancer but in order for cancer to start proliferating, a mutation must occur in any one of the somatic cells of the body. Hence, it contrasts with genetically inherited diseases such as cystic fibrosis where every cell of the body carries the mutation. According to Vogelstein, the second difference is that cancer is the combined effect of several mutations interacting with each other and not just a point mutation in one part of DNA as is typical of genetically-inherited diseases (Maxwell, 2002).

CONCLUSION

A few decades ago, no one dreamt of explaining cancer proliferation at the molecular level. In a matter of years, with the help of genetics and molecular biology, the mechanisms of cancer proliferation have been described using a molecular approach. This means that the scientific field is boosting exponentially and discoveries are made each day. This implies that a cure for cancer may not be as far as one thinks since the foundation step, that of realizing how cancer proceeds from a molecular point of view, is already laid down.

Up to now, the only treatment available for cancer is surgery, radiotherapy and chemotherapy. However, with the rates at which oncology is expanding, new drugs will be synthesized in the future, which fortunately, will find an answer to how to control cancer proliferation and if possible eradicate it.

REFERENCES

Academic Pathology, Queen's University Belfast, 2003. Neoplasia http://www.qub.ac.uk/cm/pat/undergraduate/Basiccancer/neoplasia.htm.

American Cancer Society, 2005. Oncogenes and Tumor Suppressor Genes http://www.cancer.org/docroot/ETO/content/ETO_1_4x_oncogenes_and_tumor_suppressor_genes.asp.

Collins, K. *et al*., 1997. The Cell Cycle and Cancer. Proceedings of the National Academy of Sciences of the United States of America http://www.pnas.org/cgi/content/full/94/7/2776.

Lodish, H. *et al*., 2000. Molecular Cell Biology. W.H. Freeman and Company (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=mcb.section.7090).

Mueller, R.F. and I.D. Young, 2002. Emery's Elements of Medical Genetics. 11th Edn. Churchill Livingstone.

NCBI (National Center for Biotechnology Information), 2006. The p53 tumor suppressor protein. Genes and Disease http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=gnd.section.107.

Nelson, D.L. and M.M. Cox, 2000. Lehninger Principles of Biochemistry. 3rd Edn. Worth Publishers.

Stevens A. and J. Lowe 2000. Pathology. 2nd Edn. Mosby.

Wikipedia, 2006. Cancer http://en.wikipedia.org/wiki/Cancer.

Wikipedia, 2006. Cell cycle http://en.wikipedia.org/wiki/Cancer.