Research Journal of Biological Sciences 3 (2): 251-257, 2008
ISSN: 1815-8846

The Role of Cell Cycle Regulation in Cancer

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Abstract: During the past decades, cancer research has expanded rapidly due to the relatively high incidence rate of cancer and high death rate linked to it. The type and the extent of aggressiveness of particular cancers are determined by specific flaws in the cell cycle regulation. This study gives a detailed depiction of the cell cycle's phases including the checkpoints being the G1 (GAP 1) phase, the G1/S (Synthesis) DNA damage checkpoint, the S phase, the G2 (GAP2) phase, the G2/M (Mitosis) DNA replication checkpoint, the M phase and the interphase. Regulation occurs at all the previous phases mainly through the formation of cyclins-CDKs (Cyclin Dependent Kinases) complexes. The latter control precisely the commencement and completion of the specific events leading to cell duplication and division by activating various genes such as the Rb (Retinoblastoma) gene. CDKs' activity is in turn regulated by various factors such as phosphorylation, controlled degradation of cyclins, regulated synthesis of both CDKs and cyclins by growth factors and cytokines, as well as by CKIs (Cyclin-dependent kinase inhibitors) such as p15, p16, p18, p19, p21, p27 and p57. The balance between tumour suppressor genes such as p53 and Bax and antiapoptopic genes such as Bcl2 and IGF-BP3 has also been demonstrated with a particular focus on p53-"the guardian of the genome".

Key words: Cell cycle, regulation, cancer, DNA, CDK

INTRODUCTION

Cancer is the clonal collection of cells which possess high aggressive behaviour (Fearon, 1997) and therefore it is considered to be a proliferative disease (Melnick *et al*., 1993). Such behaviour is due to genetic instability which is defined as an increase in the rate of genomic mutations caused by defects in the genes which are responsible for the checkpoints in the cell cycle. The latter genes are supposed to ensure proper genomic replication (Wodarz and Krakauer, 2001). The genomic alteration of the mentioned genes gives rise to the activation of oncogenes and the inactivation of the tumour suppressor genes (Grizzi and Chiriva, 2006). Such mutations cause stem cells to become cancerous and are therefore called Cancer Stem Cells (CSCs). CSCs retain the properties of stem cells and as a result, they are immortal and have unlimited division potential without being subjected to aging (Rajaraman, 2006).

CLASSIFICATION OF CANCERS

Cancers are usually classified according to their behaviour and thus divided into two distinct classes being benign and malignant (Underwood, 2004). However, there can be a transition from a benign to malignant state leading to metastasis and disease pathology (Wodarz and Krakauer, 2001).

Benign tumours present a slow growth rate with low mitotic activity. They are usually non-invasive and do not metastasise. In terms of histology, they have a good resemblance to normal tissue. They are often circumscribed or encapsulated and are rarely necrotic and ulcerative.

On the contrary, malignant tumours usually present high mitotic activity and are always invasive. They are usually necrotic and ulcerative and their border is often poorly defined. Their nucleus is usually hyperchromatic with multiple nucleoli (Underwood, 2004) and they metastasise frequently which metastasis occurs via the blood stream or lymphatic chains to distant organs (Dale *et al*., 2004).

Cancer epidemiology: Lung cancer was the most common cancer worldwide in 2002. Approximately 1.4 million people are diagnosed with lung cancer each year and it accounts for 12% of all cases. Lung cancer was also the most common cause of death from cancer worldwide in 2002 and accounted to 18% of all deaths from cancer. This can be seen in Fig. 1.

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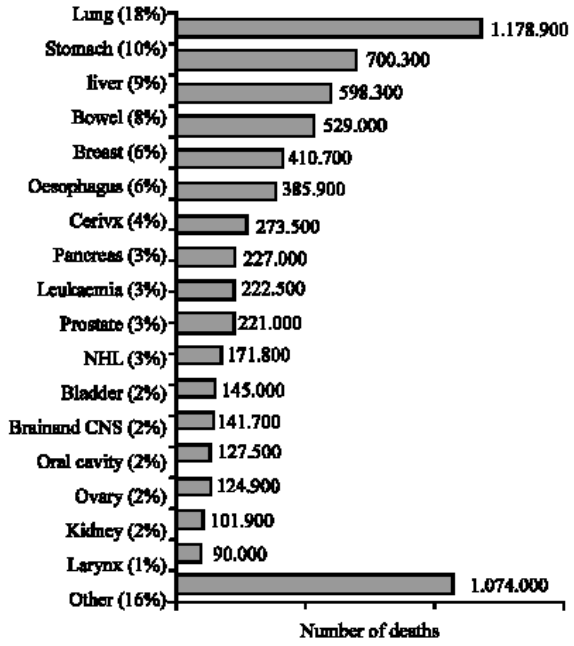

Fig. 1: The most common causes of death from cancer worldwide in 2002 (estimates) (Cancer Research, 2007)

The cell cycle: In order to understand better the physiology of cancer, the cell cycle must be studied thoroughly.

The cell cycle, which is depicted in Fig. 2, involves mainly four steps which lead to cell growth and cell division in order to produce 2 daughter cells. The phases are G1, S, G2 and M.

The G1 stage takes 10-12 h. During this stage, the cell synthesises a number of macromolecular constituents and builds up mass. It contains 2 copies of each chromosome and therefore it is in a diploid state (Underwood, 2004). Late in G1, there is the restriction point (R point) which is defined as the point after which the cell can complete a division cycle in the absence of growth factors. This point divides G1 into intervals being:

- Post-mitotic interval (G1 pm)-this spans 3 to 4 h and the cell can "opt" to exit the cell cycle and enter the G0 phase (Zetterberg *et al*., 2001). This phase is mitogen dependent (Aguda and Tang, 1999).
- Pre S-phase interval of G1 (G1 ps)-this mitogen independent phase (Aguda and Tang, 1999) spans from 1-10 h after which the cell can enter the S phase (Zetterberg *et al*., 2001).

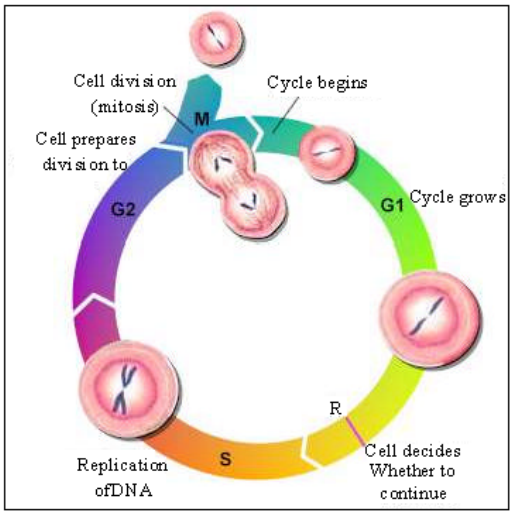

Fig. 2: The cell cycle (Darling, 2007)

During the G1/S checkpoint, DNA damage is sensed and the cell cycle is paused until the DNA is thoroughly repaired. This ensures that the S phase is embarked only when the DNA damage accumulated throughout the entire cycle has been eliminated. If the damage is so severe, apoptosis can be induced (Barbour *et al*., 2006).

In the S phase, DNA replication occurs and it takes 6-8 h. The histones and nonhistone proteins are deposited on the daughter DNA molecules to reproduce the chromatin structures. This process of doubling the genome must occur with extraordinary precision. If not, one of the daughter cells will receive a mutant genome that will threaten its ability to survive or causing it to become cancerous (Underwood, 2004).

The cell enters the G2 phase when genomic replication is complete. It now has a DNA content 4 times the haploid amount. During G_1, S, G_2 phase (Interphase) the chromatin is dispersed throughout the nucleus and is actively engaged in transcription to synthesise new proteins (Underwood, 2004).

The G2/M DNA checkpoint prevents entry into mitosis before all DNA is properly replicated and no replication forks are left (Barbour *et al*., 2006).

Mitosis (nuclear division) together with cytokinesis (cytoplasmic division) make up this phase of the cell cycle. It is further divided into phases.

Prophase: The centrosomes elaborate microtubules which attach to the cell periphery as well as to tubules from the opposite centrosome. Centrosomes start moving to the opposite poles of the cell. The chromosomes condense and can be seen as a pair of sister chromatids.

Prometaphase: The nuclear envelope disintegrates and mitotic spindle tubules attach themselves to the chromosomes' kinetochores.

Metaphase: A pause occurs whilst all kinetechores attach bipolarly to the spindle microtubules. The mitotic spindle attachment checkpoint prevents entry into Anaphase before all chromosome centromeres are bipolarly attached to the mitotic spindle.

Anaphase: Cohesins are degraded by proteolysis which results in the separation of the chromosomes by the mitotic spindle.

Telophase: The nuclear membrane re-assembles around chromosomes at the poles (Underwood, 2004).

CELL CYCLE REGULATION

The Cdk's (cyclin-dependant protein kinases) drive the events that occur during the cell cycle and can be described as the clock that times it all. In more complex cell cycles Cdk's also process information by integrating the extracellular and intracellular signals involved to allow the cell cycle to proceed despite any environmental change or mechanical failure.

The catalytic subunits of the Cdk depend primarily on the associated cyclin subunits (whose alternating concentrations cause the stage-specific timing of the Cdk) and then on protein kinases, regulatory sub units, substrate recognition and sub-cellular location. All these ensure the precise time of onset and co-ordination of the mechanical events occurring in the cell that cause cell duplication and cell division (Morgan, 1997).

Table 1 illustrates the various Cdk's involved in the entire cell cycle together with their associated cyclin and in which phase do they participate.

Table 1: Major Cdk's, their associated cyclins and the cycle phase in which they participate (Morgan, 1997)

Cdk	Cyclin partner	Role
Cdk 1 (Cdc2)	Cyclin B	M phase
Cdk 2	Cyclin E	G1/S phase
	Cyclin A	S phase and G2
Cdk 3	*	*
Cdk 4	Cyclin D	G1
Cdk 5	p35	Neural differentiation
Cdk 6	Cyclin D	G1
Cdk 7	Cyclin H	CAK/transcription
Cdk 8	Cyclin C	Transcription

*Cdk3 is closely related to Cdc2 and Cdk2. This Cdk cannot be easily detected in a mammalian cell. Its associated cyclin has not yet been identified

There are various mechanisms to regulate the CDK activity so as to control the metabolic activities inside the cell:

- Phosphorylation.
- Controlled degradation of cyclin.
- Regulated synthesis of CDK and cyclin by growth factors and cytokines.
- Inhibition of CDK (Underwood, 2004).

REGULATION AT THE G0-G1-S PHASE

Cdk4 and Cdk6 are very closely related due to their common cyclin partner (Cyclin D). Their activation gives a response to growth factors in certain cell types (they couple this with extracellular signals) (Morgan, 1997). The cyclin D-CDK4/6 assembly occurs first in mid-G1 and increases to a maximum near the G1-S transition and persist as long as mitogenic stimulation continues.

p16, p15, p18 and p19 are 4 INK4 proteins which act as CKIs (cyclin-dependent kinase Inhibitors) for CDK4 and CDK6 causing a G1 phase arrest. This demonstrates the fact that CDK4/6-cyclin D interaction is vital for passage through the restriction point and exit of G1 phase (Sherr, 1996). This occurs via the Retinablastoma (Rb) Pathway. Retinoblastoma gene is a tumour suppressor gene. Its product (Rb protein) and other Rb-like proteins such as p130 and p107 bind to E2F complexes when they are in their hypophosphorylated form and repress the E2F complexes from activating target genes required for the onset of the S-phase.

The CDK4/6-cyclin D complex triggers the phosporylation of the Rb and Rb-like proteins and therefore frees the E2F complexes which can then transactivate other genes (Sherr, 1996) required for DNA synthesis and of certain cyclins such as Cyclin E and cyclin A (Morgan, 1997). This phosphorylation is later hastened by the cyclin E-CDK2 complex showing that a positive feedback exists to enhance the rate at which Rb phosphorylation, E2F release, gene transactivation and entry to the S-phase occur (Sherr, 1996).

Rb is maintained in its hyperphosphorylated form by cyclin A and cyclin B-dependent kinases throughout the rest of the cell cycle after completion of mitosis and re-entry to the G1 or G0 phase (Sherr, 1996).

Once the S-phase is triggered, degradation of E2F and cyclin E is initiated with the latter being targeted for destruction by phosphorylation by CDK2 and then is degraded by proteolysis after ubiquination.

At this stage, a rise in cyclin A-CDK2 is also observed which prevent the interaction between DNA and E2Fs thus preventing further gene transactivation.

Cyclins D-. E- and A-dependent kinases are inhibited by the CKIs p21, p27 and p57. p27 is important in the control of the restriction point and its levels are high in cells which have exited the cell cycle (quiescent cells) since it inhibits cyclin E-CDK2 and cyclin A-CDK2 activity. The latter occurs as a result of a rise in cyclin D-CDK complexes. Translational and post-translational mechanisms control the level of p27 and its rate of turnover is increased by cyclin E-CDK2 mediated phosphorylation (Sherr, 1996).

In cancer cells, gene amplification and translocation at the D1 locus on chromosome 11q13 was observed which causes the overexpression of cyclin D1. The same happens in the case of CDK4. This was demonstrated in squamous cell carcinomas of the head and neck, esophageal carcinomas, bladder cancer, primary breast carcinoma, small-cell lung tumors and hepatocellular carcinomas. In melanoma, biliary tract and esophageal carcinomas, mutations that disable the CDK inhibitory function of the INK4a gene on chromosome 9p21 was noted. A mutation in the CDK4 which prevented interaction with p16 was found in melanoma. Homozygous deletions of the INK4a locus have also been discovered and accounted for gliomas, mesotheliomas, nasopharyngeal carcinomas, acute lymphocytic leukaemias, sarcomas, bladder and ovarian tumours. Rb loss has been linked to carcinogenesis. This has been tested on transgenic mice being Rb -/- heterozygotes which developed midlobe Rb-deficient pituitary humours. In humans, retinoblastomas, osteosarcomas, carcinoid tumours and small cell lung cancers were blamed on Rb inactivation. This also proves the fact that not all cell types are sensitive to Rb loss (Sherr, 1996). Mutations in p107 or p130 have not been found in cancer cells. Regarding to the connection of E2F with cancers, the elimination of both wild-types E2F1 allelles in mice leads to developmental defects in some tissues and to tumors in others. Humans exhibit different results since alterations in a single E2F complex might be adequately compensated. Alterations in the cyclin E and cyclin A genes in human cancers also appear to be very rare. Overexpression of cyclin E is observed in carcinomas of the breast, stomach, colon and endometrium (Sherr, 1996). The G1 checkpoint is predominantly dependent on p53 which is a tumor suppressor gene. The p53 gene is considered as the most studied tumor suppressor gene (Seemann *et al*., 2004). It accumulates when the cell is exposed to ultraviolet light, gamma-irradiation and to a range of chemotherapeutic drugs all of which cause genotoxic stress (Lane, 1992). It regulates a number of genes which are involved in cell-cycle arrest at G1 and DNA repair after detecting DNA damage before genomic replication occurs (Seemann *et al*., 2004). If the latter fails, p53 may trigger cell death by apoptosis (Lane, 1992). As a result, p53 is nicknamed "the guardian of the genome" since it prevents the propagation of defective genome to subsequent daughter cells (Speidel *et al*., 2006).

p53: The human p53 gene has been mapped on the p arm of chromosome 17 at the 13.1 locus (17p13.1). It is composed of 20 kb with 11 exons, with the first one being non-coding. It has got a number of potential sites for transcriptional regulation such as those for Sp1, NF-kappaB or C-Jun. Still, most of the protein regulation occurs at the post-translational level. It encodes for a 53kDa phosphoprotein composed of 393 amino acids. It binds DNA sequences corresponding to repeats of RRRC(A/T)-(T/A)GYYY (R is a purine, Y is a pyrimidine). The protein has got five structural domains:

- N-terminal transactivation domain.
- Proline-rich regulatory domain.
- Sequence specific DNA binding domain.
- Oligomerisation domain (Seemann *et al*., 2004).
- C-terminal domain involved in DNA binding which can be upregulated by phosphorylation (Mowat, 1998).

The DNA binding domain consists of beta-sheets that supports flexible loops and helixes that are in direct contact with DNA. A zinc atom interacts with the mentioned loops and helixes and stabilises them. In cancer, mutations of this structure are observed which include the inhibition of protein-DNA contacts and the disruption of protein folding (Seemann *et al*., 2004).

The p53 gene is a facultative gene since it is almost dormant in most cells and it is susceptible to degradation by proteasomes after ubiquination. Mdm2 is a ring-finger protein which interacts with a short domain in the N-terminus of p53. It affects the p53 in three ways:

- It exports it out of the nucleus (which is its location of action) into the cytoplasm
- Inhibits the activation of p53-dependent gene by preventing it from binding to transcriptional machinery therefore masking its expression. This occurs since the Mdm2 gene binds to the transcriptional activation domain of p53.
- Induces the binding of ubiquitin chains to lysines located on the C-terminus of p53 making it susceptible to degradation by proteasomes

An auto-regulatory mechanism is observed in the interaction between p53 and Mdm2 where the latter gene is activated by the p53 itself. When the p53 protein rises, an increased activation of the Mdm2 gene is observed which in turn deactivates the p53 protein and therefore reducing its levels to normal values.

Overexpression of the Mdm2 gene increases the degradation of p53 and therefore increasing the cell's susceptibility to cancer (Seemann *et al*., 2004). 17 out of 47 human sarcomas show this behaviour (Lane, 1992).

Stabilisation of the p53: The p53 protein can be stabilised through various pathways in response to DNA damage being phosphorylation by stress-signalling or growth signalling kinases such as Casein Kinase 1 (CK1), Casein Kinase 2 (CK2), Checkpoint Kinase 2 (Chk2), Ataxia Telangiectasia Mutated kinase (ATM), Ataxia Telangiectasia mutated Related kinase (ATR), Protein Kinase C (PRKC), c-Jun N-terminal kinase (JNK) and Mitogen-Activated Protein Kinase MAPK and acetylation by co-activator histone acetyl transferases such as p300. The main pathway involves the sensing of DNA damage by the ATM kinase and phosphorylation of p53 at the Mdm2 binding site and the disruption of p53-Mdm2 interaction and therefore leading to p53 nuclear accumulation (Seemann *et al*., 2004).

Another important pathway for the control of p53 involves p14 which expression is activated in response to growth stimuli and controlled by the E2F1 transcription factor. p14 binds to Mdm2 and restrain its location within the nucleolus and as a result, free p53 can be released in the nucleus (Seemann, 2004). A deletion of the p14 gene results in the removal of inhibition on Mdm2 and therefore p53 degradation is kept under control. Tumours in the brain, breast and lungs might exhibit such behaviour (Vogelstein, 2000).

p53 activity: Once stabilised, p53 can trigger both transcription dependent and transcription independent pathways. Transcription independent pathways include the binding to components of DNA replication/repair machinery such as the helicases ERCC2 and ERCC3 while transcription dependent pathways include the genetic activation of:

- Cell cycle regulators in the G1 and G2 phases-eg. p21.
- Regulators of apoptosis-eg. BAX, FAS, Bcl-2, IGF-BP3.
- Genes involved in cellular response to stress-eg. NOS2 and COX2.
- Genes involved in DNA repair (O6-methylguanine methyltransferase (O_6MGMT) and MSH2) (Seemann *et al*., 2004).

Mutations of p53 linked to cancers: Mutations of p53 have been observed in all types of cancers but they vary with different cell types. In for example cancers of the aero-digestive tract, TP53 is mutant in up to 75% of the cases of invasive cancers (Seemann *et al*., 2004).

Seventy five percent of TP53 mutations are missense of which 80% are located within the sequence encoding the DNA-binding domain of the protein. There is only a 2% chance of a mutation in the C-terminal and N-terminal (Seemann *et al*., 2004). A deletion of the carboxy-terminal domain prevents the formation of p53 tetramers and is found in occasional cancers at many different sites (Vogelstein, 2000).

At least two mutated residues in the transactivation domain (Amino-terminal) are required to disrupt the p53 transcriptional activity.

In the DNA-binding domain, mutations have been observed in the majority of the residues although some are more frequent than others. These disrupt the protein-DNA interactions. Such an example is the amino acid changing mutation in this domain which will prevent p53 from binding to defective DNA sequences and is observed in colon, breast, lung, bladder, brain pancreas, stomach and oesophageal cancers amongst others (Seemann *et al*., 2004).

Its important to note that not all p53 mutations pave the way for cancers. Such mutations are called "silent mutations" and account for 4.4% of all mutations (Seemann *et al*., 2004).

ERCC2 and ERCC3: ERCC2 and ERCC3 form part of a TFIIH complex having both kinase and helicase activity. The TFIIH complex plays an important role in transcription and in DNA excision repair. p53 in its wild-type and mutant form inhibits both the ERCC2 and ERCC3 in vitro, thus initiating apoptosis. Fibroblasts with mutated ERCC2 and ERCC3 experienced reduced level of binding and therefore inhibition by p53 resulting in reduced apoptosis.

$p21^{WAF1/CIP1}$: The $p21^{WAF1/CIP1}$, which is considered to be a Cyclin dependent Kinase Inhibitor (CKI), is activated by p53 and inhibits effectively the G1/S cyclin dependent kinases Cdk2, Cdk3, Cdk4, Cdk6 kinases and inhibits weakly the G2 active cdc2 kinase (CDK1) (Mowat, 1998).

$p21^{WAF1/CIP1}$ can also be activated via p53 independent pathways by inducing interaction of transcription factors with the p21 promoter. This induction occurs by various agents such as phorbol ester (PMA), okadoic acid, the tumour suppressor protein BRCA1, transforming growth factor-β (TGF-β), calcium, butyrate, lovastatin, histone deacetylase inhibitor Trichostatin A (TSA) and Nerve Growth Factor (NGF) (Blundell, 2006).

$p21^{WAF1/CIP1}$ is also involved in the transcription control of the PIG3 gene which is involved in the ROS pathway. Once activated, the PIG3 gene induces reactive oxygen species which are released from the mitochondria resulting in cell apoptosis (Macip *et al*., 2002).

If proliferation is considered, $p21^{WAF1/CIP1}$ was found to either promote or inhibit this process depending on the

specific cellular context. An increase in tumorogenesis was observed in $p21^{WAF1/CIP1}$ knockout mice (Blundell, 2006) due to the interruption of the G1/S checkpoint.

Bcl2 and Bax: The Bcl2 gene is considered to be an antiapoptopic gene. The Bcl2 protein inhibits apoptosis and this was demonstrated in the differentiation of myeloid cells into granulocytes where its levels decrease and they underwent apoptosis (Naumovski *et al*., 1996).

In contrast, the Bax gene, which is a member of the Bcl-2 gene family is considered to be an apoptopic gene. It is activated by p53 since p53 DNA-binding sequences have been found in the Bax gene promoter. Overexpression of p53 gives rise to increase in Bax gene expression and direct increase in Bcl-2 gene repression (Mowat, 1998). The Bax protein increases the mitochondrial membrane permeability and stimulates cyt c release into the cytoplasm which activates the caspases enzymes (Jürgensmeier, 1998).

Caspases are a class of proteases which degrade essential cellular proteins and thus inititate apoptosis. They can also couple with death receptors in the membrane such as Fas and TNFR (Tumor Necrosis Factor). The Fas receptor is upregulated by the p53. The docking of the Fas ligand to the Fas receptor was found to induce apoptosis in activated T-lymphocytes. Downregulation of Fas receptor as a result of loss of p53 will interrupt cell death in tumors (Mowat, 1998).

IGF-BP3 (Insulin Growth Factor 1-Binding Protein 3): Insulin Growth Factor 1 (IGF-1) binds to the IGF-1 receptor to stimulate survival, differentiation and proliferation (Misawa *et al*., 2000). It can suppress apoptosis induced by the overexpression of the Myc oncogene. The p53 upregulates the expression of IGF-BP3 which will bind to IGF-1 and prevent it from docking to its receptor. p53 also directly represses the activity of the IGF-1 receptor gene. Therefore, the cell's susceptibility to apoptosis is increased. Mutations in p53 causing its disability will result in the increase of IGF-1 receptors and the tumor cell will be protected from apoptosis (Mowat, 1998).

Regulation at the interphase: At interphase, Cdk7 is one of the major Cdk-Activating Kinases (CAK). These phosphorylate the Cdk subunit for complete activation. The Cdk7-cyclin H complex is associated with the transcription factor TFIIH. Thus here it can act as a kinase that phophorylates the RNA polymerase II C-terminal domain during the process of transcription. This shows the involvement of Cdk7 in transcription and the cell cycle.

Regulation at the G2/M phase: For instance, Cyclin B and Cyclin A bind to $p34^{cdc2}$ (also known as CDK-1) and induce the activation of $p34^{cdc2}$ by triggering the critical dephosphorylation of the kinase especially Thr-14 and Tyr-15. The active $p34^{cdc2}$-cyclin B complex functions as the Mitosis Promoting Factor (MPF) as it initiates mitosis.

p53 is also involved in the control of the G2/M phase. It has been demonstrated that the cell cycle was blocked at the G2/M phase as a result of the overexpression of the Mos oncogene and members of the MAP kinase pathway (including activated Ras, Raf and MEK oncogenes) which pathway is dependent on p53. Centrosome duplication also falls under the control of p53. This has been demonstrated in p53 deficient cells where multiple copies of centrosomes and changes in the spindle checkpoint control have been observed. This resulted in the disruption of normal chromosomal separation (Mowat, 1998).

Expression of telomerase: The expression of telomerase may also lead to carcinogenesis. Telomeres are non-coding repetitive sequences found at the ends of chromosomes (Weinstein and Ciszek, 2002). In humans they consist of TTAGGG repeats to form linear tandem arrays (Zhong *et al*., 2007). These sequences have a protective role as they prevent the chromosomes from fusing into rings and also prevent them from binding to other DNA sequences, thus maintaining their stability and integrity (Weinstein *et al*., 2002; Zhong *et al*., 2007). This explains why any telomere loss leads to somatic cell line mortality. Telomeres shorten with every cell division by 50 to 150 base pairs (Zhong *et al*., 2007) as the enzyme molecules are unable to reproduce completely the chromosomal ends (Weinstein *et al*., 2002). This does not affect cellular function until a point has been reached where at least one of the telomere sequences has become critically short (Weinstein *et al*., 2002). This leads to the disabling of the replicative mechanisms (Weinstein *et al*., 2002) and withdrawal from the cell cycle (Zhong *et al*., 2007) and therefore cell aging.

Telomerase is a reverse transcriptase which elongates telomere sequences, by using its RNA template to add Guanine rich repeats to the 3' end, (Gümüs-Akay *et al*., 2007; Weinstein *et al*., 2002) while acting together with telomere-binding proteins (Weinstein *et al*., 2002). Studies have shown the link between telomeres, telomerase and cancer since the telomerase is therefore inactivating the aging process and leading to cell immortality or tumorigenesis (Weinstein *et al*., 2002). This is shown by the fact that most cancer cells are capable of preventing telomere shortening by means of the activation of either telomerase, a telomere maintenance mechanism, or alternative lengthening of telomeres. The enzyme telomerase is strongly suppressed in human

somatic cells but its activity is resumed in highly proliferative tissues as well as in cancer cells (Zhong *et al*., 2007).

REFERENCES

Aguda, B.D. and Y. Tang 1999. The kinetic origins of the restriction point in the mammalian cell cycle. Cell. Proliferation, 32: 321-335.

Barbour, L., L.G. Ball, K. Zhank and W. Xiao, 2006. DNA Damage Checkpoints are Involved in Postreplication Repair. Genetics, 174: 1789-1800.

Blundell, R.A., 2006. The biology of $p21^{Waf1/Cip1}$-Review Paper. Am. J. Biochem. Biotechnol., 2: 33-40.

Cancer Research UK, 2007. Viewed 28 February 2007, http://info.cancerresearchuk.org.

Dale, D.C., D.D. Federman, K. Antman, J.P. Atkinson, C.K. Cassel, M. Feldman, R.J. Gibbons, R.B. Haynes, J.B. Henrich, M.J. Holtzman, M.G. Lebwohl, W. Levinson, D.L. Loriaux, S. Ruddy and J.S. Wolinsky, 2004. ACP Medicine. 2004-2005 Edn. American College of Physicians, USA.

Darling, D., 2007. Viewed 19 February 2007, <http://www.daviddarling.info/encyclopedia/C/cell_cycle.html>.

Fearon, E.R., 1997. Human Cancer Syndromes: Clues to the Origin and Nature of Cancer. Science, 278: 1043-1050.

Grizzi, F. and M. Chiriva-Internati, 2006. Cancer: Looking for simplicity and Finding Complexity. Cancer Cell International, Vol. 6.

Gümüs-Akay, G., A.E. Ünal, S. Bayar, K. Karadayi, A.H. Elhan, A. Sunguroglu, and A. Tükün, 2007. Telomerase activity could be used as a marker for neoplastic transformation in gastric adenocarcinoma: But it does not have a prognostic significance. Genet. Mol. Res., 6: 41-49.

Jürgensmeier, J.M., Z. Xie, Q. Deveraux, L. Ellerby, D. Bredesen and J.C. Reed, 1998. Bax directly induces release of cytochrome c from isolated mitochondria. Preoc. National Acad. Scie. United States Am., 95: 4997-5002.

Lane, D.P., 1992. p53, guardian of genome. Nature, 358: 15-16.

Macip, S., M. Igarashi, L. Fang, A. Chen, Z.Q. Pan, S.W. Lee and S.A. Aaronson, 2002. Inhibition of p21-mediated ROS accumulation can rescue p21-induced senescence. Embro. J., 21: 2180-2188.

Melnick, R.L., J. Huff, C.J. Barrett, R.R. Maronpot, G. Lucier and C.J. Portier, 1993. Cell Proliferation and Chemical Carcinogenesis: Symposium Overview. Environ. Health Perspectives, 101(Suppl 5): 3-8.

Misawa, A., H. Hosoi, A. Arimoto, T. Shikata, S. Akioka, T. Matsumura, P.J. Houghton and T. Sawada, 2000. 'N-Myc induction stimulated by insulin-like growth factor I through mitogenactivated protein kinase signaling pathway in human neuroblastoma cells. Cancer Res., 60: 64-69.

Morgan, D.O., 1997. Cyclin-dependent kinases: Engines, clocks and microprocessors. Ann. Rev. Cell Dev. Biol., 13: 261-291.

Mowat, M.R.A., 1998. p53 in tumour progression: Life, death and everything. Adv. Cancer Res., 74: 25-48.

Naumovski, L. and L. Clean, 1994, Bc12 inhibits apoptosis associated with terminal differentiation of HL-60 myeloid leukemia cells. Blood, 83: 2261-2267.

Rajaraman, M., D.L. Guernsey, M.M. Rajaraman and S.R. Rajaraman, 2006. Stem cells, senescence, neosis and self-renewal in cancer. Cancer Cell International, Vol. 6.

Seemann, S., D. Maurici, M. Olivier, C.C. de Fromentel, and P. Hainaut, 2004. The tumor suppressor gene TP53: Implications for cancer management and therapy. Critical Rev. Clin. Lab. Sci., 41(5-6): 551-583 pp: 551-560.

Sherr, C.J., 1996. Cancer cell cycles. Science, 274: 1672-1677.

Spiedel, D., H. Helmbold and W. Deppert, 2006. Dissection of transcriptional and non-transcriptional p53 activities in the response to genotoxic stress. Oncogene, 25: 940-953.

Underwood, J.C.E., 2004. General and systematic pathology. 4th Edn. Churchill Livingstone, United Kingdom.

Vogelstein, B., D. Lane and A.J. Levine, 2000. Surfing the p53 network. Nature, 408: 307-617.

Weinstein, B.S. and D. Ciszek, 2002. The reserve-capacity hypothesis: Evolutionary origins and modern implications of the trade-off between tumor-suppression and tissue-repair. Experimental Gerentol., 37: 615-627.

Wodarz, D. and D.C. Krakauer 2001. Genetic instability and the evolution of angiogenic tumor cell lines (Review). Oncol. Reports, 8: 1195-1201.

Zetterberg, A., S. Ekholm, F. Erlandsson and P. Zickert, 2001. Growth control, cell cycle control and the restriction point' (Abstract). Cell Biology International, Vol. 25.

Zhong, Z.H., W.Q. Jiang, A.J. Cesare, A.A. Neumann, R. Wadhwa and R.R. Reddel, 2007. Disruption of telomere maintenance by depletion of the MRE11/RAD50/NBS1/ complex in cells that use alternative lengthening of telomeres. The Journal of Biological Chemistry, Manuscript M701413200.