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The process of Cell Division Mechanism: Normal cell versus Cancerous Cell

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Abstract: This review article insights about 17 papers to understand the mechanism of a normal cell division and the role of cyclin and CDKs complexes in the cell division. It also highlights the roles of tumor suppressor and oncogenes in a cancerous cell and the pathways that can get affected in breast and lung cancer.

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1.0 Introduction

Cells are the basic unit of our life. Human body grows with the help of the basic process which occurs inside our body that is cell division. In this review article we will get to know what happens to a cell at molecular level during its division, how a normal cells differs from the cancerous cell and what happens in a cancerous cell. Chromosomes are thread like structure made of proteins condensed with DNA wrapped around. During the cell division this chromosome undergoes a lot of changes and form a new identical cell, but how the part of a cell chromosome knows when to divide. Genes are the basic unit of a specific segment of a DNA which encodes a specific genetic product such as RNA, proteins. We can say that gene serves as an engine to promote the cell to produce specific proteins. The specific proteins produced are further used for signalling pathways so that the cell communicate with each other.[1,2] There are many signalling molecules (ligand) such as proteins, growth factors, lipids, ions and binds with the receptors present in the cell membrane.[3]

The pathway is a set of complex steps: Ligand binding, Phosphorylation, Activation/ Inhibition of many molecules, Activation of Transcription Factors, Production of proteins.[2] Some examples for the signal transduction pathways are RAS, RAF, MAP kinase pathways. All these pathways are a series of complex steps occurring for the production of variety of targets like protein kinases and transcription factors (TF).[4]The end product of this transcription factor is a production of protein by stimulating and inhibiting gene expression. The

protein produced from this transcription factor helps in the process of embryogenesis and development of an embryo.[5]Cyclin and cyclin-dependent kinases (CDKs) are the proteins which aids in the cell cycle division for a cell to grow. A somatic cell in our body uses mitosis as its division to grow and differentiate and if the cell's DNA is exposed to any kind of mutagens, ionizing radiations these cells do not enter the mitotic phase.[3]Cell division and cell death are two important cellular processes in a self-regulating organism.[6] Let us move on the cell cycle difference of a normal cell v/s a cancerous cell.

1.1 Cell Cycle of a normal cell

As of now we have read the importance of cell regulation in a person. Let us now dive into the cell cycle and next more deeply into its molecular level. The cell cycle is divided into four successive phases:G_0- G_1,S,G_2,M .The G_0, G_1, S, and G_2 together are called the interphase and the M phase is known as the Mitotic phase.[6]The G_0phase is the quiescent phase where the cells of our body remains on hold for a long period of time, but some of the quiescent cells can re-enter the cell cycle through the stimulation of hormonal or growth factor.[3,6] The $G_1$and G_2 are the gap phase that occurs between the two important landmarks S (DNA synthesising) and mitosis (M) phase.The G_1 is the phase where the cell prepares itself for the next S phase. The cells in the G_1 phase do not possess or have a pair of sister chromatids hence no replication of DNA takes place. S phase also known as synthesis phase, the crucial step where the DNA replication takes place. The G_2 is the second gap phase prior to S phase, here the cell prepares itself for the next mitotic phase. This phase doesn't have pre-replication complexes which are required to initiate DNA replication, hence DNA replication can take place only in S phase.[3,7]Now, if the cell progress to next phases without being examined this may promote a wrong cell to divide. To know whether the cell has properly undergone each phase we have checkpoints programmed in our cell cycle. These checkpoints ensures that the cell will not move on to the next process unless and until the present process is completed. After moving to the next process it has no way of going back. These checkpoints are to confirm proper DNA replication, proper summation of chromosomes to each daughter cell formed[3, 6]. The checkpoints in a cell cycle include: Two that record the sincerity of DNA and halt cell cycle either in G_1 or G_2 (Restriction checkpoint) .One which make sure that the DNA is properly synthesized before the beginning of mitosis. One documenting the chromosome alignment during anaphase (Spindle Assembly Checkpoint).Till now we can say that a cell cycle is regulated by **two** controls:

1. Introduction of growth factor and then this signal if satisfies the conditions set down the genes, ensuring cell division.
2. Checkpoints of the cycle monitors the righteous conditions of the genome and the previous completed cell cycles(Figure no 1).[8]

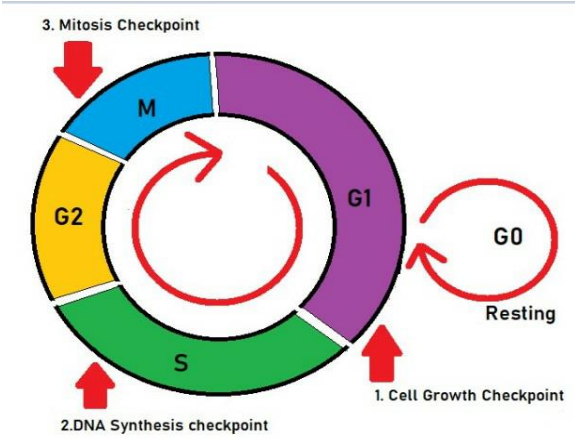

Figure no 1: Cell Cycle and its Checkpoint

1.2 Cell Cycle Regulatory Proteins

The cell cycle is regulated by both positive and negative pathways in our human system.[3, 8.] The positive pathway include cyclin and cyclin-dependent kinases. CDKs are serine/threonine kinases and are regulated by the interactions with cyclins and CDK inhibitors. There are 7 CDKs which regulates cell cycle (CDK1, CDK2, CDK3, CDK4, CDK5, CDK6, and CDK7) and CDK7 to 11 mediates gene transcription. The cyclin-CDKcomplex regulates the cell cycle via phosphorylation of the targeted genes. This cyclin-CDK complex is activated by mitogenic signals and is inhibited by checkpoints in response to DNA damage. Genetic alterations like mutations, being exposed to mutagens, carcinogens in this regulatory proteins (cyclins, CDKs) leads to uncontrolled cell proliferation which ultimately leads to cancer(Figure no. 2).[3, 6]

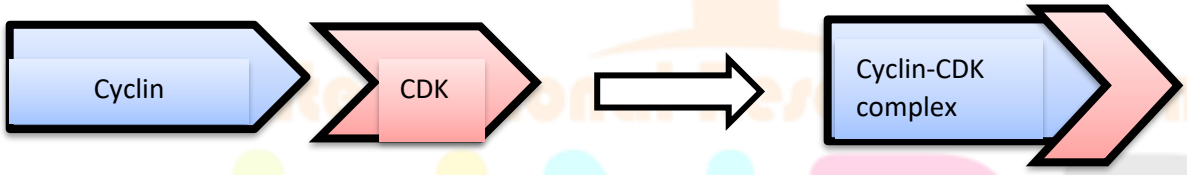

Figure no 2- Cyclin and CDK complex formation

The negative pathway includes cyclin dependent-kinase inhibitors (CKIs). Two families of CKIs have been observed: a) CDK interacting protein (Cip)/Kinase inhibitory protein (Kip): This family is involved in regulating cell cycle by inactivating many cyclin-CDKs complexes hence blocking the cell cycle. This family further has three members of proteins :P21/ Cip 1/ waf 1/ sdi 1,P27/ Kip 1,P57/ Kip 2.The second class of family is INK 4 proteins. These are the tumour suppressor proteins that is it regulates cell division, keeping it under proper check. INK4 proteins restricts the progression of cell cycle by binding and connect with cyclin D/CDK4/6(Table no.1).

Table no 1- The INK4 further have four members of proteins: P16, P15, P18, P18.

CKI PROTEIN FAMILY	MEMBERS
1. Cip/Kip	P21/Cip 1/ waf 1/ sdi 1 P27/ Kip 1 P57/ Kip 2
2. INK 4	P16 P15 P18 P19

1.3 Cell cycle control in mammalian cells: Role of cyclin-CDK complex

The first cyclin-CDK which is switched on after the quiescent stage (G_0) is cyclin D with CDK4/6. Cyclin D is absent in the cells of the G_0 phase, as discussed previously G_0 cells expression can be stimulated by mitogenic/growth factors. CDK4/6 drives cell cycle progression from G_0 or G_1 phase to S phase with association of cyclin D1, D2, and D3. This cyclin D/ CDK 4/6 complex is essential for crossing restriction points. Active complex of cyclin D/ CDK 4/6 initiates phosphorylation of tumour suppressor proteins like Retinoblastoma (RB) protein, p107, p130 which plays an important role in negative control of cell cycle. RB proteins supresses the transcription of genes which are regulated by E2F transcription factor inhibiting G_1/S transition. The E2F induces the transcription of G_1/S target genes like cyclin E, CCNA, CCNB, spindle check point protein MAD2. The function of RB protein is to inactivate E2F and stop the DNA from replication, this further stops the cells to pass through the G_1 checkpoint. RB protein is inactivated by phosphorylation. If RB protein is mutated it starts producing protein which does not binds to E2F whether it phosphorylates or not(Figure no 3)**.** [6, 8, 9]

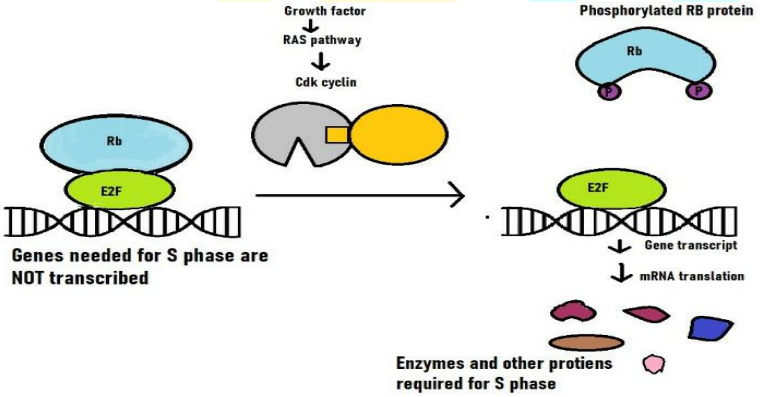

Figure no 3: Regulation of the RB protein

Cyclin E other protein starts synthesizing from the mid phase of G_1 and gets peaked in the late G_1 phase (restriction point). During the late G_1 phase activated E2F genes (Cyclin E1 and E2) activate CDK2 by binding it. Cyclin E/CDK 2 plays a role in the later phase and pushing the cell into the S phase of the cell cycle. It is observed that in some tumours cyclin D1 and E is overexpressed. Cyclin E is degraded by F-box protein after being entered into S phase and the CDK2 then gets associated with the Cyclin A. Cyclin A/CDK 2 assists DNA replication and is vital during the S phase of the cycle. The phosphorylation of CDC6 and E2F1 takes place by the complex cyclin A/CDK2 terminating the S phase and beginning of the G_2 phase. The bustle of cyclin A/CDK 2 peaks till the G_2 phase of the cycle. The cyclin A activates CDK 1 which makes the cells to enter the mitotic (M) phase of the cycle. Cyclin B/CDK1 complex maintains the activity of CDK1. The breakdown of nuclear envelope, assembly of mitotic spindle, condensation of chromosomes which all occurs in the M phase of cycle is bought up by the phosphorylation of activated CDK1. There is a decrease in the activity of CDK1 through the degeneration of the cyclin B by APC. The degenerated expression of CDK1 helps in chromosome separation, cytokinesis, and completion of mitosis. Then the cells departure the cell cycle and makes an entry to the permanent or reversible G_0 phase regulated by cyclin C/CDK3.[6, 8, 9] Overview of cyclins and CDKs:G_1 phase - Cyclin D + CDK4/6 ,G_1 / S phase - Cyclin E + CDK 2, S phase – Cyclin A + CDK 2, G_2 / M phase – Cyclin A + CDK2/1,M phase – Cyclin B + CDK 1(Figure no 4).

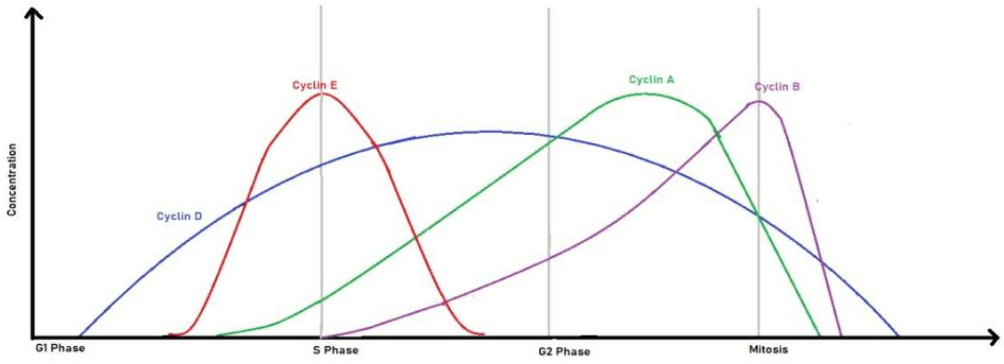

Figure no 4: Cyclin and CDK Complex Concentration at different phases of cell cycle

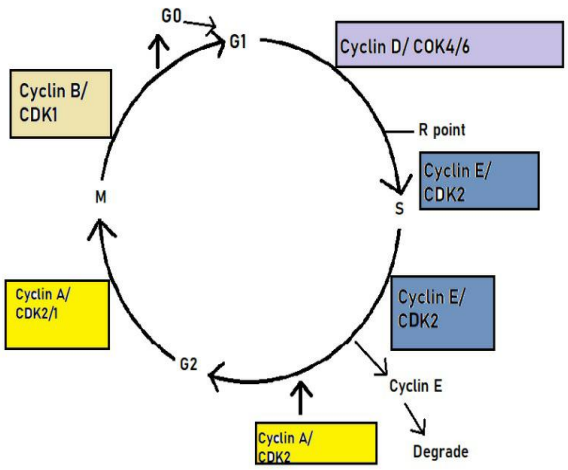

Figure 5: Cyclin and CDK complexes at different phases of cell cycle.

2.0 Genes Promoting Cancer

2.1 Oncogene

The transforming genes which transforms the normal cells to a malignant cells is the oncogene. Proto-oncogenes are the one which encode proteins that regulates a normal cell to grow regularly in a well-mannered. The mutated form of a proto-oncogene is the oncogene. Oncogene proteins activates the signals even in the absence of external mitogenic/ growth factors. In short, Oncogene mutated form of proto-oncogene.Let's take an example of the RAS proto-oncogene and oncogene.

The protein produced by the RAS proto-oncogene awaits for the external signal at the cell surface and when the wait is finished the primary signal in turns releases excess of secondary signals deep in the cell. Whereas, the protein produced by the RAS oncogene works differently it releases the secondary signals deep in the cells without being getting activated by the primary signals. Now the cell is with excess growth stimulatory signals which results in cell proliferation leading to formation of tumors.

Some examples of oncogenes are MYC, LMYC, and RAF.[8, 10]

2.2 Tumor Suppressor Genes

These are the growth-suppressing genes which plays a character in tumorigensis. The proteins produced by the tumor suppressor genes allows the cells to progress a negative signal that is halt the cell division. A cell losses its ability to divide and to respond to the external mitogenic growth signals if the cell has loosed a tumor suppressor gene. The most common example is the Retinoblastoma gene (RB) which we just discussed previously. The other most common example is the TP53 gene. The TP53 gene encodes for a tumor suppressor protein and it has been observed that this gene is inactive in many of the human cancers. The function of TP53 gene is to protect cells against the development of cancer. The functional protein of the TP53 gene is the P53 protein.

TP53 (gene) ⟶ P53 (protein)

At the post transcriptional level p53 an inducible protein gets activated when a cell is in a stressful condition leading to formation of DNA damage. The DNA damage activates the transcription factor p53 protein and the signalling pathway gets started.P53 regulates proteins and genes which are involved in :Cell cycle arrest,Repair Apoptosis, Replication, transcription**.**P53 protein accumulation leads to the arrest of cell cycle either in G_1 (before DNA replication) or in G_2 (before entering into mitosis). This arrest helps the DNA to repair by activating enzymatic DNA repair system, it also induces apoptosis. A mutant p53 gene can't maintain the integrity of its genome as the cell does not receives the signal for cell cycle arrest, the result is less cell stable, uncontrolled cell proliferation with greater malignant potential**.**[6, 10, 11, and 12]

3.0 Molecular Biology of Breast Cancer

The uncontrolled cell growth, dysregulation of cyclin-CDKs, disabling of cell-cycle checkpoints are the main causes of forming tumors and breast cancer. Cyclin D/CDK 4/6 governs the retinoblastoma phosphorylation and promote the cell to divide, the dysregulation of cyclin D/CDK4/6, and E2F pathway leads to formation of tumors and breast cancer. It has also been observed that the loss of Cip/Kip family proteins function, amplification of CDK4/6 are responsible for biological functions in breast cancer. Cyclin C- CDK3 complex which is associated with G_0/G_1 cell cycle transition contributes to cell proliferation, migration and apoptosis. Genes including for the breast cancer are BRCA1, BRCA2 which are located on chromosome 17 and 13 respectively. Germ line mutations in BRCA1 & 2 leads to breast and ovarian cancer. The cell surface tyrosine kinase receptor – human epidermal growth factor receptor (EGFR), HER2 binds with the growth factor and if mutated promotes cell proliferation, angiogenesis, metastasis, and preventing apoptosis. It has been observed that HER2 is overexpressed in 25-30% of breast cancer patients(Figure no 6).

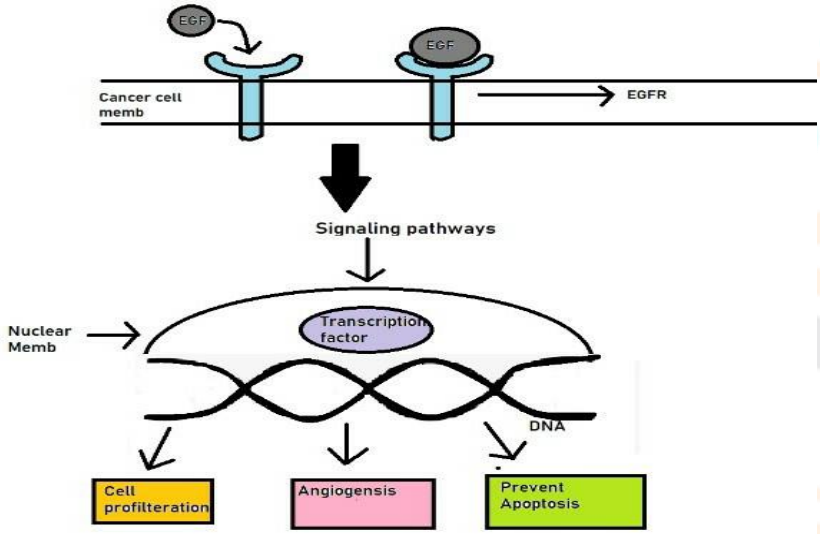

Figure no 6: A brief of signalling pathway promoting breast cancer.

The tumor suppressor p53 nuclear phosphoprotein maintains cell cycle, repair DNA, inhibition of angiogenesis, apoptosis. Mutation in this gene causes 20-40% of sporadic breast cancer too.[6, 13]

4.0 Molecular Biology of Lung Cancer

Lung cancer is the leading cause of death in men and women around the world. The two types of lung cancer non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) have been identified on the basis of their difference in the genetic alterations. NSCLC also includes adenocarcinoma, squamous carcinoma, and large cell carcinoma. The alteration in the oncogenes is the cause of many cancers. The activation of growth promoting proteins like: KRAS,EGFR,BRAF,MEK-1/ MAPK-1,HER 2.The inactivation of tumor suppressor proteins like P53,LKB-1,PTEN.This are the causes of lung cancers, let us study some of the pathways.

4.1 KRAS Pathway

This belongs to the family of RAS proto-oncogenes. The mitogenic signal to a receptor activates the healthy KRAS protein activating number of downstream mitogenic proteins (MAPK, RAS, RAF, MEK, MAPK) pathway which sends a message that tells the cells to divide. Mutated KRAS becomes hyperactive and can't switch off any more. Mutated KRAS is the common cause of lung cancer. Common mutation in KRAS in Smoker is G□T trans-version. Non-smoker is G□A transitions(Figure no 7).

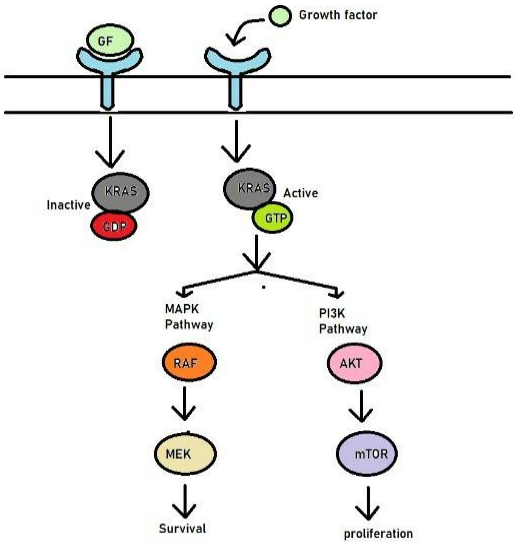

Figure no 7: A brief of normal KRAS signalling pathway.

4.1.1 Epidermal growth factor receptor (EGFR)

Epidermal growth factor receptor (EGFR) has an extra and an intracellular tyrosine kinase domain. Mutation in EGFR have shown the development of multiple lung adenocarcinoma (ADC). EGFR mutation occurs in the first four exons of intracellular tyrosine kinase domain, second common EGFR mutation is the missense mutation (change in one DNA base pair). In lung cancer all EGFR mutations occurs in ADC(Figure no 8).

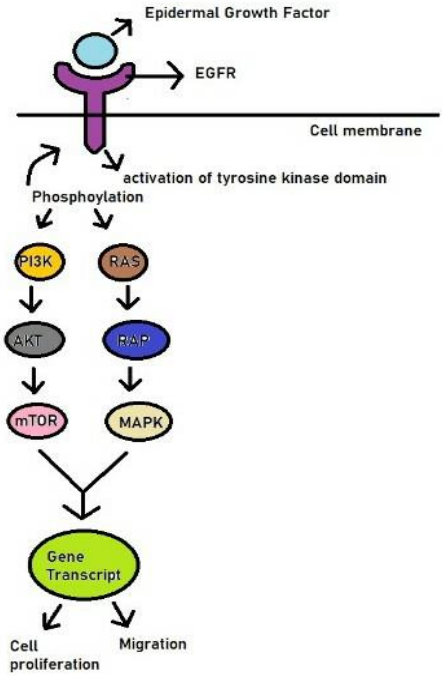

Figure no 8: A brief of normal EGFR signalling pathway.

4.1.2 Tumour suppressor gene: LKB1 (STK 11)

The gene LKB1 is located on chromosome 19 and the protein synthesised from this gene inhibits mTOR by disrupting the pathway and its components. This has been more commonly seen in 30% of adenocarcinomas than squamous carcinoma .The tumor suppressor gene RB1 whose protein RB (retinoblastoma) regulates cell cycle from G_1□S phase is also found to be inactive in small cell lung carcinomas (SCLC).[14,15]

5.0 Conclusion

In summary, this paper paves to know the cascade of event how a cell divides, how a gene encodes for a protein that helps in the cell division. Cyclin-CDK complex controls the cell cycle progression by phosphorylating target genes, the activation of cyclin-CDK complex occurs by the induction of some mitogenic or growth factor signals and the inhibition takes place in response to DNA damage and by the cyclin

dependent-kinase inhibitor (CKIs) families. There are two genes that promotes abnormal cell division viz cancer oncogenes and the tumor suppressor genes. The working of a P53 gene which helps in the apoptosis is the most prevalent example studied. Some of the genes including for breast cancer are BRAC 1 and 2, the cell proliferation, promotion of metastasis, prevention of apoptosis leads to formation of tumor and metastasis takes place. Intensive ongoing research has aquiented the world with various treatments to combate cancer, some of them include chemotherapy (use of chemical drugs to kill the cancer cells), radiation therapy (use of radiation doses to kill the cancer

cells), surgery, immunotherapy (use of medications that boost up the immune system to fight against the cancerous cells)[16].Targeted therapy like use of monoclonal antibodies is among the top now when compared with chemotherapies and has proved effective in combating cancer cells[17]. More and more research needs to be done on the diagnosis more advanced being molecular biological and bioinformatics.Though we have many

different treatment are available as listed above, however there in a need to work on newer and molecular approaches to treat cancer**.**

Conflict of Interest: None

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