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Role of Tumour Suppressers and Oncoprotein in Cancer Biology: A Review Paper

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ABSTRACT: Tumour cells were fused with normal Somatic cells to make hybrid cells. The Suppression of Tumorigenicity in these hybrid cells prompted researchers to hypothesize that genes within the normal Somatic cell had inhibitory actions to stop tumour growth. In health tissues, Cell-to-Cell contact in dense cell populations acts as an inhibitory factor on proliferation. This contact inhibition is typically absent in many cancer cell populations. Growth-inhibitory factors can modulate the cell cycle regulators and produce activation of the CDK inhibitors, causing inhibition of the CDKs. Loss of restriction by disruption of pRBregulation can be found in human tumours, which produces a loss of restraint on transition from G1 to S phase of the cell cycle. Disruption of TP53 function causes results in the affected cell accumulating genomic defects. Down-regulation of p21 and p27, which can be found in tumours with normal TP53 function.Oncogenes acts as inducers of tumour Angiogenesis. During tumour progression, an angiogenic switch is activated and remains on, causing normally quiescent vasculature to sprout new vessels continually that help sustain expanding tumour growth. Angiogenesis is governed by a balance of pro-angiogenic stimuli and angiogenesis inhibitors, such as thrombospondin (TSP)-1, which binds to transmembrane receptors on endothelial cells and evokes suppressive signals. A number of cells can contribute to the maintenance of a functional tumour vasculature and therefore sustain angiogenesis. These include pericytes and a variety of bone marrow-derived cells such as macrophages, neutrophils, mast cells and myeloid progenitors.
The most striking example of successful immunotherapy is that with rituximab, an antibody against the common B-Cell antigen CD20.

KEYWORDS : Tumorigenicity, Angiogenesis, Autophagy, Amplification, Isoprenylation

I. INTRODUCTION :

Tumour Suppressor gene have role to reduction of cell functions during mutation. Caretaker genes involves in the stability of genome via DNA Repair, Gatekeeper Genes including basically apoptosis and Landscaper genes promotes unregulated proliferation.

According to molecular basis of cancer; Protooncogene is origin of Oncogene. By formation of mutated protein by mutated Oncogenes can be result in 3 ways like No change in protein content or activity ; or increased protein content or activity (Positive mutation); or decreased protein content or activity (Negative mutation). In cell; Protooncogene act as Accelerator when it muted in this case the positive mutation can lead cancer. In the other hand, Tumour suppressor genes act as break when it muted in this case the negative mutation can lead cancer.

The article highlights the evidence that Tumour formation and development are characterized by individual processes, working synergistically, and an understanding of each individual process may provide a better basis for further anticancer research.

The 1st Classic tumour suppressor gene by Alfred Knudson, known as the Rb gene, which codes for the Retinoblastoma tumour suppressor protein. Oncogenes coding for growth factor, Truncated growth factor receptors, non-receptor Tyrosine kinases, Protein and DNA binding Protein. Two-hit hypothesis involves which states both alleles that code for a particular protein must be affected before an effect is must be affected before an effect is manifested. If only one allele for the gene is damaged, the other can still produce enough of the correct protein to retain the appropriate function (Mutant tumour suppressor alleles are usually recessive, whereas mutant oncogenes alleles are typically dominant).

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- Involved Mechanisms for the Activation of Protooncogenes:

In the activation of protooncogenes included mechanisms are

(1) Mutations ; alteration in the function of the gene protein product (ras genes). May interfere with the splicing of transcribed Pre mRNA. Within the gene mutation cause change in the function activation, stability and location of proteins.

(2) Chromosomal translocation ; example of possible resulting product –gene/protein fusions, disable genes, Create errors which genes by insertion of transposable elements. It occurs near the sites for C-myc and C-mos. These are 8:14 in 90% of Burkitt's lymthoma and 8:21 in acute myeloid leukemia respectively.

(3) Genes amplification is accompanied by two cytogenic changes : Double minute chromosome and homogeneously staining regions (HSRs). Most frequently amplified oncogenes are N-myc and C-myc. Others are C-Ki-ras, C-myb, C-abl and C-erb B. Amplifications of gene is accompanied by roughly proportional increase in number of Transcripts. Deregulated cell growth by gene Amplification of C-myc may decrease the tendency of promyelocytic leukemia cells to differentiate in culture.

(4) Insertional mutagenesis may operate if regulatory elements of a virus are inserted in proximity to cellular protooncogene. There is evidence that proviral integration in lymphomas can occur in the region of C-myc.

- Genes Associated With Apoptosis :

Apoptosis is mediated by proteolytic enzymes called caspases which trigger cell death by cleaving specific proteins in the cytoplasm and nucleus. Caspases exist in all cells as inactive precursors, or procaspases, which are usually activated by cleavage by other Caspases, producing a proteolytic Caspase Cascade. Apoptosis and Autophagy Regulatory Events; both are acting Antagonistic to each other. But they both act in cell death mechanism.

1. An intrinsic pathway which is associated with the mitochondria Beta cell lymphoma 2 (BCL 2), Casecade 9 and Akt.
2. The Extrinsic pathway where the death receptors are involved on the surface of the cell.

Both mechanisms get activated when there is the increase in the level of the Cascade 3 and Akt which ultimately lead to apoptosis of the cell and do cell death.

- (P53) Gatekeeper oncoprotein and bcl-2 gene in Apoptosis :

As molecular basis of cancer; Positive mutation of Protooncogenes and Negative mutation of Tumour Suppressor Genes lead cancer. Transcription factors growth factors; cell proliferation and ultimately by some related pathways apoptosis can regulated.

Commonly,In case of 13 chromosomal Rb genes which is located in nucleus by inactive transcription attachment can active the gene. By growth factors due to increases of CDK Kinase formation and the conversion from ATP to ADP by Cyclin D – CDK4/6, Cyclin E – CDK2, Cyclin A – CDK2 ; phosphorylation occurs which make the gene inactive and detachment of Active Transcription factor, results in cell proliferation occur.

Causes of activation of P53 are oxidation stress, Nutritional deficiency, hypoxia, oncogene expression, DNA damage, Ribosomal Dysfunction, Telomere Attrition. Damaged DNA activate ATM/ATR and by the involvement of checkpoint kinase in conversion from inactive to active P53 gene a pathway continue for working on DNA. As the result, PUMA inhibit Bcl2. For that it can't inhibit apoptosis.

The bcl-2 gene product may function in an anti-oxidant pathway but the exact mechanism is uncertain.

- Antibodies and Inhibitors' involvement into Immuno and Targeted Therapy :

The Concern with selective targeted agents is that parallel signalling pathways can compensate for the inhibition of a single kinase and resistant mutations can quickly develop. Conversely, with multitargeted kinase inhibitors, there are issues with off-target effects leading to toxicity. Also, because multiple pathways are affected, there is a poor understanding of the true mechanism of these agents in a particular tumour, making it difficult to develop further improvements in specificity or activity.

Besides phosphorylation, other posttranslational protein modifications have been identified as targets for cancer therapy. One of the easiest attempts at this strategy was inhibition of RAS isoprenylation by farnesyltransferase inhibitors.

Chaperone protein represent a unique class of therapeutic target. The chaperone machinery plays an important role in protein homeostasis by facilitating nascent protein maturation and holding.

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In precision medicine; small molecule drugs and monoclonal Antibodies are involved. Basically this therapy works on too much of a certain protein on a cancer cell, abnormal protein cell or mutated protein cells that aren't normal working.

So in that case, The main actions are :-

1. To block chemical signal to turn off the cell growth and division.
2. To change proteins for resulting Apoptosis.
3. To stop making new blood vessels to feed the cancer cell.
4. To trigger immune system to kill the uncontrolled cell.

For these working ; Angiogenesis inhibitor, monoclonal Antibodies, Proteasome inhibitor and Signal Transduction inhibitors have to involved.

On the other way; in immunotherapy; There have different way like Checkpoint inhibitors, Chimeric Antigen receptor (CAR) T cell Therapy, Cancer vaccine, Monoclonal Antibodies (mAbs or MoAbs), Oncolytic Virus, Immunomodulators, Cytokines.

Checkpoint inhibitors stop the ability of cancer cells to stop the immune system from activating and in turn, amplify your body's immune system to help destroy cancer cell. Common Checkpoint inhibitors follow PD-1/PD-L1 and CTLA-4 pathways.

II. CONCLUSION :

This Review Paper is an evidence of the importance to avoid the negative mutation of Tumour suppressor and positive mutation of protogenes. Enzymatic circumstances in the continuing pathways which are involved in the mutation and the process are important to understand for further research. Around 80% of detected cancer-related mutations are in tumour suppressor genes. However, targeting tumour suppressors has been long though to be challenging or even unlikely in some cases. Despite many failed attempts in the past, scientists have been hoping to find novel approaches and techniques to restore the level and activity of tumour suppressors or the signalling pathways they initiate. In particular, advances in cancer genomics have greatly improved the prospects for new drug discovery and re-evaluation of existing drugs and compounds. In a new era of precision medicine, many efforts are anticipated to improve comprehensive assessment of various subsets of heterogeneous cancer by integrating advanced genome sequencing, new bio informatic and biostatistical tools and humanized preclinical models.

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