ORIGINAL RESEARCH PAPER

oncology

UNDERSTANDING OF MOLECULAR ONCOLOGY FOR RADIATION ONCOLOGIST FOR UPCOMING ERA OF CONCURRENT TARGETED RADIOTHERAPY

KEY WORDS: Targeted Therapy, mutations, Radiotherapy.

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ABSTRACT

The process by which normal cells become progressively transformed to malignancy is now known to required the sequential acquisition of mutations which arises as consequence of damage genome of cells this damage can occurs as a result of endogenous process such as, The replications of DNA by free radicals generated during metabolic process, DNA can also get damage by external agents such as ionizing radiations ultraviolet rays as well as chemical carcinogens ,The new discipline by precisely identifying the molecular basis of differences between normal and malignant cells.

The new concepts of cancer management by targeted therapy alone as well as along radiotherapy further makes this very important to understanding by oncologist specially radiation oncologist since targeted therapies to target altered genes and if goes a step ahead to specific targeted therapies for specific types of mutations happened in DNA

DISCUSSION

Cancer cells are those cells that can overcome the boundaries impending unrestrained division will multiply, and in turn sustain the opportunity to acquire further aberrations that fuel its growth, survival, invasion and migration (Metastases) to establish its presence in distant organs. .So we require to understand complex Process that dictate cell cycle and cell division, survival of cancer cells its migration and invitation at tissue level, we must define target cell population and understand the interaction of with its local and systemic environment including mechanism governing response of associated fibroblasts, immune cells and vasculature, finally we need to identify the complex feature that establish cancer at primary "organs" and distant site, including and physiologic effect and the establishment of a blood supply (Angiogenesis).

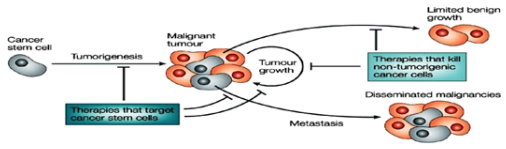

FIG- TUMOR CELL PROGRESSION AND METASTASIS

Technologies have emerged that facilitates understanding of pathways which gets disturbed leading the cause of cancer further leading the concept of therapies that targets specific molecules within the pathways along with diagnostic stratification of patients based on identification of those disturbances provider the Potential to revolutionize cancer management like few examples are. Gleeve which inhibits a subset of tyrosine kinase is approved for the treatment of CML and Gastrointestinal stromal tumors (GIST)

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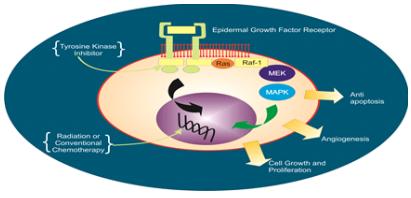

FIG-VARIOUS STEPS AT WHICH TUMOR GROWTH CAN BE STOPPED

IRRESA which inhibits EGFR is approved for treatment of NSCLC, Herceptin an antibody drug that inhibits Erb B2 (Her-2-Neu) is used for treatment of Her 2 – positive breast cancer.

VELCADE – A Proteosome inhibitor that elicits programmed cell death (Apoptosis) is approved for treatment of multiple myeloma many more targeted compounds & Biological are currently under trials.

HISTORICAL BACKGROUND

Molecular basis of cancer came from the study of viruses that could cause cancer in experimental animals, first cancer- causing virus, Rous sarcoma virus (RSV a Retrovirus) was identified in 1911 by "Frances Peyton Rous" for that he was given Nobel Prize in 1966.

Molecular basis for RSV- causing cancer, found that viral src oncogene was revealed by series of culture cell experiments, V-src is the homolog of a cellular proto-oncogene (C-Src) was a conceptual milestone which opened the floodgates for the discovery of numerous proto-oncogene's with homology to viral oncogene for above work J. Michal Bishop and "Harold E Vermus" got a Nobel Prize in 1989.

Early work with viruses and oncogenes led to the development of numerous cell culture assays for specific properties of cancer. Which ultimately led to the discovery of many additional oncogenes. Same way the assay quantifies foci of piled cells that result from "transformation" of an initially contact inhibited cells. In early 1980s Ha-ras and K-ras genes were discovered in foci resulting from transfection of immortalized mouse fibroblasts with human cancer cell line DNAs. The C-ras genes were subsequently shown to be homolog's of respective sarcoma virus oncogenes. The focus formation assay has instrumental in discovering cooperating effects of oncogenes and in the assessment of certain tumor suppressor genes (TSGs).

Another avenue for cancer gene discovery was development of " Cytogenetic Study" here identification of specific chromosomal translocation study leads to discovery of fusion gene that encode oncogene Philadelphia example is BCR –ABL oncogene encoded by translocation between

FIG- VARIOUS NEWER AGENTS HOW THEY STOP TUMOR GROWTH

chromosome 9 & 22 (the protien translocation) and frequently present in CML.

Evidence for tumor suppresser gene activity initially came in picture after study of fusion cells that contains two different phenotypes normal verses tumor genomes study carried out in vivo tumorogenic potential cells implantation subcutaneously in to immune compromised mice, study shown that normal genomes (which having tumor suppressor gene) could override the cancer cell phenotype indicating the presence of dominant tumor suppresser activity.

RBI gene (Retinoblastoma) was identification 1986.
RBI gene as a gene deleted or truncated in sporadic and familial retinoblastoma was first TSG cloned by mapping inactivating genomic alterations. Soon after P53 gene was discovered P53 gene found as tumor suppressor gene known to be in activated by specific DNA tumor virus proteins.

THE MOLECULAR BASIS OF CANCER

Research and study on gene - Restriction fragment length polymorphism-based positional based positional cloning, termination tremendous technological advances have fueled an explosion of knowledge about the pathways and mechanisms that drive cancer. Collectively, these technologies provide us with strategies that promise to transform cancer management in the clinic.

As result now human genomic study gene up to unprecedented level, genomic sequence study and protein analysis can provide vital information and help in help defining." Molecular Signatures" associated with specific type of Cancer till now 25000 human gene sequence finalized & study along with their DNA sequences representing specific gene, now most promising port of study that stratify tumor based on specific gene (called as molecular signature) in several cases these molecular signatures have been identify that correlates with prognosis.

Study also gene to Access DNA Methylation status and/or the modification of specific histones or other regulatory proteins associated with specific gene regions. Many key changes within the tumors occur at level of post translational regulation via protein modification such as phosphorylation, these may result in the alteration of activity, stability, however there is no way to access their changes globally, but these parameters must be monitored by inside method that depending on the availability of specific antibodies per for immunodetection.

FUNCTION STUDIES OF CELL CULTURE SYSTEM

Cell culture systems continue to provide an avenue for probing potential cancer mechanisms. Both primary cell cultures (isolated from fresh tissue) and established cell lines are used. The focus formation and soft agar colony assays are classic methods used to assess loss of contact inhibition and encourage independent growth. Respectively. Basic assays for cellular migration and invasion through extracellular matrix components are also widely used. The advantage highly sophisticated microscopy and image analysis tools has facilitated thousands of small molecules and genes can be monitored that modulate specific type of cancer, induction of apoptosis or migration and its critical pathways and thus potential drugs target can be identify.

Cell culture findings must ultimately be assessed in an appropriate in vivo setting. The mouse is the most widely used mammalian system for such studies. The traditional approach, as previously mention is the transplantation of cells into recipient immune compromised mice, when cells derived from human tumor cell lines and engrafted mice are referred as xenograft, the most common approach is the simply implant the cell subcutaneously however in many cases cells can be transplanted in to the tissue of organ called as orthotropic transplantation they provide more about microenvironment influencing the tumor.

It is clear now that tumor microenvironment coevolves with cancer cells that even orthotropic transplantation may not accurately reflect many things that is the immune system which play important role in cancer genesis.

The mouse in which tumor arises spontaneously within the tissue of origin provide the most accurate method of study of etiology of cancer, carcinogen treated mice provide avenue for study tumorogenesis, many carcinogen preferentially induce tumor, at specific sites, offering the possibility of reproducibility. Example wild type mice Azoxy-methane cause colon cancer with histological and genetic similarity to human colon cancer.

CANCER MECHANISMS

During the development the complex and highly regulated mechanism ensures that appropriate number of cells produced with in every organ during the process as abnormal cells undergoes apoptosis another highly regulated intrinsic cell distraction process, during all these the process is regulated by cell cell interactions as well as signals from local microenvironment, many cells must migrate via extracellular matrix to arrive at appropriates destinations .

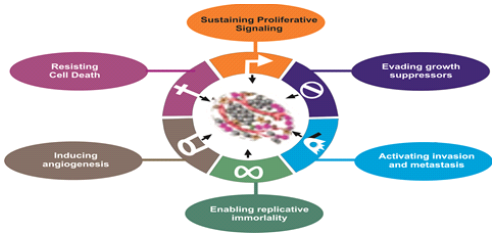

FIG-SEPTS WISE PROGRESSION OF TUMOR GROWTH

There above Process continue as ongoing dynamic Process for example hematopoietic cell / GIT mucosal lining/skin or as response to abnormal conditions resulting in tissue inducible liver regeneration or wound healing.

CANCER GENES

Gain of function of oncogenes and losing function in TSG (Tumor suppresser gain) result in the development cancer, as per data more than 1% of genes (291 out of total estimated and found gene 25000) may contributed to some form of cancer.

70% of these genes are affected by somatic with mutations.
20% of these genes are affected by germ line mutations.
10% of these genes are affected by both.

Dominant mutations comprises 90% of somatic mutations most of these 70% are associated with translocation identifying the genes (oncogenes) resulting from translocation,(in haemopoitic or mesenchymal malignancies) There could be many more oncogene in contrast to somatic mutations, 90% of germ line mutations in familial caner syndromes are in TSGs, kindly because most dominant oncogene mutations would cause lethality during development and will result in cell death.

Oncogene or TSG gene expressive affected by epigenetic modifications such as methylation or chromatin organization but there are some genes act both ways as oncogenes or TSG depending on the timing or context in which they function best example is transforming growth factor (TGF) β., TGF β is a growth inhibitory cytokine but growth inhibition is only one of its many effect, cell proliferation and apoptosis, during tumor progression, tumor cells frequently lose the growth inhibition response to TGF β and associated with an increase expression of TGF β in microenvironment apart from oncogenes there are many genes and gene combination act as modifiers and do have impact on cancer cells behavior that's is why some smoker never developed lung cancer, or some patients never develop metastasis or some respond well to therapies some do not.

CELL CYCLE REGULATION

Cell cycle have different phases G0G1 S G2 M, cell cycle clock serve as master regulator of this Process , disturbance of protein involved

in cell cycle regulation can lead to cell growth which turn promote tumor genesis. Cell cycle regulated by cycline dependent kinas', cycline are synthesized at the beginning of phase and destroyed at the end of their phase of cell cycle.

Each step of cell cycle is monitored by "molecular check point gene" like P53 gene (tumor suppressor gene) frequently mutated in different cancers, P53 protein is a DNA binding transcription factor, That can induce during (Stress to cell) Various factor to arrest cell growth apoptosis, and finally Cell growth arrest.

CELLULAR APOPTOSIS AND AUTOPHAGY

When during cell division DNA damages occurs or mutations occurs the process of cell death initiated ,apoptosis regulated by TNF factor protein other pathways are internal signaling leading to cell apoptosis, the mitochondrial mediated pathways involves the release of Cytochrome C from mitochondrial membrane regulated by gene bcl2 the antiapopotosis gene and activation of p53 gene which is proapoptotic gene Apoptosis not only programmed cell death happens side by side second program also works called as autophagy in this program cell destructions happens when cell suffers nutrient starvation, cell digest their own intra cellular organelle by cytoplasmic lysosome gene involved here is BECLINE-1 tumor suppresser gene, autophagy also controlled by nutrients sensing mTOR kinase

ANGIOGENISCS

In order tumor cells to progress , they must acquire angiogenic ability, like normal tissue, tumor tissue require an adequate supply of oxygen, nutrients, also an adequate way to remove waste products thus gaining access to the vascular system and generation of tumor blood supply are considered as rate limiting step in tumor progression.

Induction of angiogenesis depend upon anti and proangiogenic factors, these factors centre induced and activated by release of multiple molecule release by cancer cells.

In order to progress of tumor cells, over expression of proangiogenic factors and under expression of (or down regulation of) antiangiogenic factors is very important step, like members of VEGF proved to be significant proto oncogenes apart from VEGF other factors help in angiogenesis are, IL-8, angiopoeitin, PDGF (Platlet derived Growth Factor) growth factor all of them served to promote formation of blood vessels, in search of targeted therapies antiangeogenetic factors are attractive targets.

INVASION AND METASTASIS

Only 10% cancer patient's death happens due to primary cancer, 90% death occurs due to metastasis of primary cancer and Cancer spreads by two ways.

a) Invasion
b) Metastasis

Concurrent Radiotherapy and Targeted therapy

The newer concepts developing that using targeted therapy in low dose daily prior to radiotherapy like concurrent chemo radiotherapy similarly EGFR positive locally advanced head and neck cancer , by using Gafitinib or Elrotinib in locally advanced NSCLC lung cancer under phase two and phase three trails , and concurrent radiotherapy along cetuximab an monoclonal antibody have been proved to be effective in increasing overall survival rate in locally advanced head and neck cancers .

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