

## Molecular Signalling Saga in Tumour Biology

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### ABSTRACT

'Cancer' is a broad term used for malignant tumours that has spread throughout the body. The initiation and progression of tumour is driven by complex signaling pathway that can be majorly categorized as oncogenic signal and anti-oncogenic signal. The development of tumour is regulated by abnormal oncogenic signal. The therapy of tumour is designed via targeting the blockage of oncogenic signal or activation of anti-oncogenic signal. This review is an illustration of different signaling pathway involved in tumour biology and the timeline historical review of progress made in the field of tumour biology.

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**Key words:** Cancer; Tumour; Signalling in Tumour; Molecular Basis of Tumour development

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### INTRODUCTION

#### 1. WHAT IS CANCER?

'Cancer' is a broad term used to describe a group of more than hundred diseases characterized by abnormal cells giving rise to a lump or mass of tissue called as Tumor or Neoplasm. The term 'carcinoma' or 'carcinoma' was coined by Hippocrates (Father of Medicine) to describe cancer. Development of cancer is a result of persistent unregulated cell proliferation in the body of affected person<sup>[1]</sup>. Here cells do not respond properly to the signals corresponding to normal cell behavior and surpass the 'programmed cell death' which involves self destruction of damaged and worn out cells or when a cell no longer continues to function under the restraints of the cell cycle and proliferate continuously<sup>[2]</sup>. As a consequence tumor formation takes place which can be categorized as Benign or Malignant depending on the invasion potential of a cell (Figure 1). When a tumor is restricted to one place showing limited growth then it is termed as Benign but if the tumor starts to invade nearby tissues via lymphatic system or circulatory system (blood and lymph) then the tumor is said to be malignant and the process is termed as Metastasis<sup>[3]</sup>. The subsequent loss of growth control is the ultimate result of accumulated aberrations in numerous cell regulatory systems that affects cell behavior and discriminate cancer cells from normal cells.

#### 2. TYPES OF CANCER

There are more than hundred distinct types of cancer based on the originating cell types. The affected cells differ widely in their response and behavior towards the applied treatments. Any anomalous cell proliferation is a tumor that can be benign or malignant as discussed above. However, both types of tumor possess characteristic feature of unregulated cell proliferation but only malignant tumors are designated as cancer as it is much more dangerous than benign tumors. It is tough to treat malignant tumors

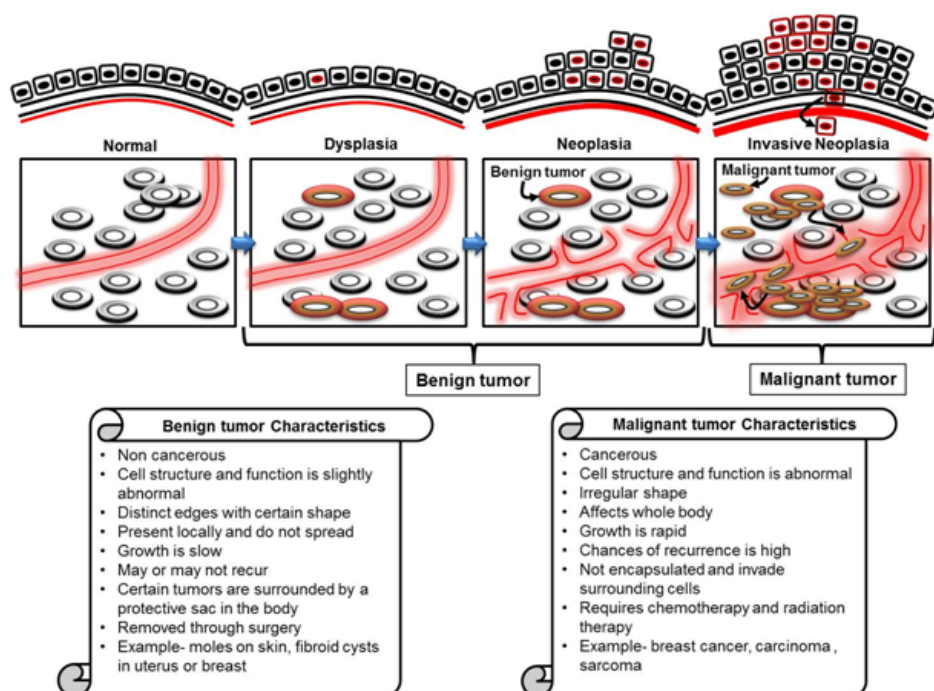


Figure 1 Stages of tumor development and characteristics of Benign and Malignant tumor.

due to their invading and metastatic property, while benign tumors can be treated surgically<sup>[4]</sup>. They are classified on the basis of type of cells where they originate for instance, colon and breast cancer etc.

Cancer can be categorized under three main groups i.e. (1) carcinomas: malignant tumor of epithelial cells contributing to 90% of human cancers; (2) leukemias and lymphomas: cancers of blood forming cells and immune cells contributing to 8% of human cancer and (3) Sarcomas: malignant tumor of connective tissues those are very rare in humans. Prominent cancers accounting for more than half of the cancers are breast, prostate, lung and colon/rectum where lung cancer is the most lethal attributing for approx. 30% of all cancer deaths<sup>[5]</sup>.

### 3. EARLY THEORIES ABOUT CANCER

Most ancient theory for the cancer is proposed by Hippocrates (Father of medicine) during 300-400BC named as Humoral theory which stated that out of the four body fluids- blood, phlegm, yellow and black bile; it is black bile whose increased level in body cause cancer. Later Zacutus Lusitani and Nicholas Tulp concluded that cancer is contagious i.e. infectious disease theory proposed in 1600s. Moreover in 1700s Stahl and Hoffman hypothesized that cancer was a consequence of fermenting and degenerating lymph and called it as lymph theory. Then after a century in 1838 Johannes Muller hypothesized that cancer initiates from cells instead of lymph and proposed that cancer develops as a budding elements (i.e. blastema) among normal tissues, thus recognised as blastema theory. Another theory i.e. parasite theory stated that cancer spreads with the help of a parasite. Then came chronic irritation theory stated by Virchow that cancer arises from chronic irritation and it spreads like a liquid, but later in 1860 Karl Thiersch showed that cancer cells metastasize due to malignant cells instead of unidentified fluid flow. Some scientists inspite of developing understanding about cancer between 1800s-1920 believed that injury i.e. trauma is the cause of cancer, known as trauma theory. A different scientist S. Paget in 1889 stated that tumor cells are like seed which shows some specificity for certain

organ called as soil and malignancy depends on the compatibility of both seed and soil while F. Rous in 1910 identified that virus can cause cancer in chicken and proposed Viral theory. Then came the mutational theory proposed by T. Boveri which is the widely accepted theory at present age that mutations in somatic cells responsible for cell proliferation and controlling cell cycle is the cause for cancer. Moreover developmental timeline research in the field of cancer has been shown in figure 2.

### 4. TUMOR DEVELOPMENT AND PROGRESSION

Most cancers exhibit a single abnormal cell origin that is monoclonal origin which has been identified with the help of X chromosome inactivation analysis. For instance, X chromosome inactivation happens randomly during embryonic development where inactivation of one X chromosome takes place in some cells whereas other X chromosome inactivation in other cells. Thus in females with heterozygous X chromosome gene, expression of both the alleles take place in normal tissues whereas only one allele is expressed in tumor tissues which signify the monoclonal origin of tumor cells<sup>[6]</sup>. Cancer is known to be originated by either genetic changes (mutations) or by change in pattern of gene expression. Most cancers are initiated by genetic changes in somatic cells while nearly only 1% in germinal cells. Transition of a normal cell into cancerous cell (i.e. Transformation) is a multi-step process that involve three distinct phases i.e. initiation, promotion and progression. Initiation is the first step where normal cells acquire changes that enable them to form tumors while promotion is the second step where cell proliferation takes place of initiated cells. Lastly, proliferated cells acquire additional genetic changes that impart them malignancy and metastasis. Thus affected critical genes play a crucial role in driving the process of tumorigenesis<sup>[7]</sup>. Moreover the factors that cause these genetic changes are called carcinogens that mean cancer causing agents.

**Carcinogens or cancer causing agents:** Carcinogens are cancer causing agents that can be divided into various categories

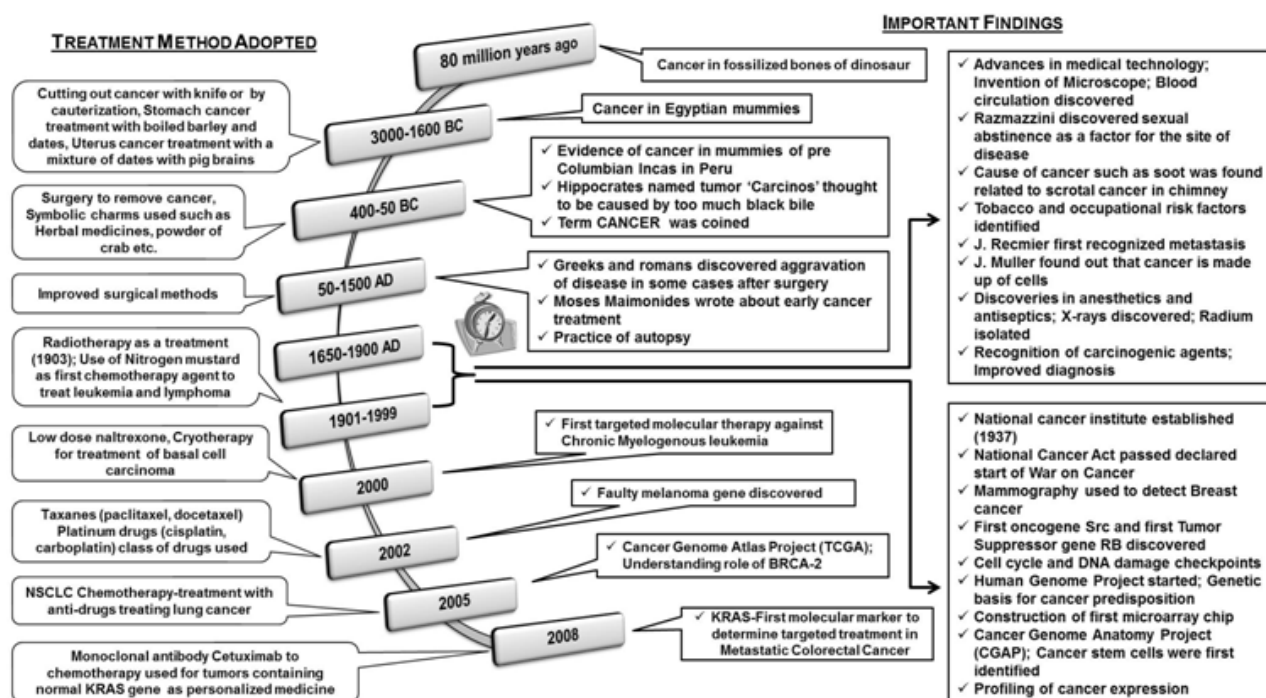


Figure 2 Timeline research in Cancer.

depending on their sources, for instance Environmental, Genotoxic, Human, Chemical and Occupational carcinogens. In general these carcinogens induce DNA alteration that in turn promote cell division and suppress cell apoptosis. Such an example is environmental carcinogens (pesticides, tobacco, food chemicals and chemicals from industries) that disrupt the action or elimination of the hormones in the body, their release, transport and metabolism which is known to cause prostate cancer, breast cancer, testicular cancer and uterine leiomyoma<sup>[8]</sup>. Another is Genotoxic carcinogens which are DNA interacting electrophiles [2-AAF (2-acetamide fluorine), 3'-Me DAB (3'-methyl dimethyl-amino azo benzene), DEN (N-nitrosodiethylamine)] that covalently interact with DNA and thus formed complex results in DNA damage. Moreover human carcinogen (e.g. Bile acid) acts as a cancer promoter in human gastrointestinal cancer which includes cancer of stomach, small intestine, esophagus, liver, pancreas, colon and rectum. It produces reactive oxygen species and cause oxidative stress that damage the DNA thereby making cell resistant towards apoptosis<sup>[9]</sup>. Furthermore chemical carcinogens for example Parabens is used as food preservative, personal care products and as pharmaceuticals that has the potential to cause human breast epithelial cells cancer<sup>[10]</sup>. Lastly occupational carcinogens such as organic dust, metals, combustion products, inorganic dust, mineral oils, crystalline silica, aromatic amines, radon and solar radiation found at working place are known to cause various cancers<sup>[11]</sup>.

## 5. MOLECULAR BASIS OF CANCER

Cancer critical genes are the genes that are responsible for causing cancer which contributes to the process of transformation where elevated cell proliferation, insensitivity to cell death and differentiation has been observed. Such genes drive the processes of cell cycle progression, cell differentiation, DNA repair and cell death<sup>[12]</sup>. These cancer critical genes can be classified into two broad categories, (1) **Oncogenic**: Genes that require gain of function for causing cancer that involve *proto-oncogenes*, *metastatic genes* and *angiogenic genes* while on the other hand, (2) **Anti-oncogenic**:

Genes that require loss of function for causing cancer that involve *tumor suppressor genes* and *apoptotic genes*. Moreover, mutations in cancer critical genes could be dominant or recessive, for instance proto-oncogene possess dominant mutation i.e. require mutation only in single copy for its effect while tumor suppressor genes exhibit recessive mutation i.e. they require mutation in both copies of genes for its inactivation.

**Proto-oncogenes**: These are the genes that control the normal process of cell growth and division. Proto-oncogenes encoded proteins are generally growth and transcriptional factors, growth factor receptors and signal transducers that govern the process of cell proliferation and suppressed cell death. Proto-oncogenes upon functional gain mutation become oncogenic in nature and thus cause cancers. E.g. *EGFR*, *myc*, *src*, *Wnt* etc.<sup>[13]</sup>.

**Metastatic genes**: These are the genes that impart invasion and dissemination property to the cancerous cell. E.g. *MMP2/9*, *COX2* etc.<sup>[14]</sup>.

**Angiogenic genes**: These are the genes that aid and drive the formation of new blood vessels. In response to the growth factors secreted by cancerous cell, neovascularization take place around the tumor to provide oxygen and nutrients for tumor cell proliferation. E.g. *VEGF*, *bFGF*, *PDGF* etc.<sup>[15]</sup>.

**Tumor suppressor genes**: In general tumor suppressor genes are known to restrain the cell division rate and thus have a role in preventing tumor progression. They often undergo mutational inactivation in cancerous cell. E.g. *p53*, *BRCA1/2*, *PTEN* etc.<sup>[16]</sup>.

**Apoptotic genes**: These are the genes that govern programmed cell death of unwanted, damaged or dangerous cells in multicellular organisms. E.g. *Bax*, *Bak* etc.<sup>[17]</sup>.

Oncogenic signals include oncogenes, metastatic genes, angiogenic genes and anti-oncogenic signals include tumour suppressor genes, apoptotic genes. There is an intricate interplay between these genes which signals for either cell proliferation or inhibition of cell proliferation and secrete chemical signal for tumour initiation and progression.

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## SIGNALING PATHWAYS IN CANCER: AN INTRICATE INTERPLAY AMONG GENES

‘Chemical signals’ are the basis of communication among the cells that trigger the cascades to control their cellular environment and division. All ‘signaling pathways’ possess three common characteristic features that include a chemical messenger, a receptor and a cellular response. A signaling pathway gets activate upon the reception of a chemical signal (e.g. a hormone, growth factor) at the matching receptor present on cell surface. The binding of chemical signal triggers the receptor to conduct signals to interior of the cell which further activate the messenger proteins. Moreover, these messenger proteins carry the signals through cytoplasm via activating protein kinases that further induces the signaling cascade. Most of the signaling pathway ultimately transmits the message to the nucleus and cell organelles like mitochondria. Cancer is a consequence of multiple cell-signaling breakdowns that affects the cellular homeostasis and alters the apoptotic process while triggering uncontrolled cell proliferation. The affected cell signaling pathways causing cancer are as follows:

**Affected signaling pathways in cancer:** The signaling pathways governing cell differentiation and proliferation aberrantly get affected in cancer. They are complex interlinked signaling networks that are involved in regulating the process of cell growth, cell death, angiogenesis and metastasis in tumor cells<sup>18</sup>. For instance, PI3K-Akt, mTOR, JAK-STAT, ErbB, MAPK signaling pathways have a role in tumor survival and growth i.e. cell proliferation, evading apoptosis and sustained angiogenesis. Moreover Wnt, Hedgehog and Notch signaling pathway also has a role in controlling cell fate determination and development. While p53, Rb, PTEN pathway<sup>[19-24]</sup> has a role in suppressing tumor survival via cell damage repair or ultimately apoptosis of the damaged cell. Whenever the level of oncogenic signals are higher, it signals for abnormal cell proliferation otherwise anti-oncogenic signal suppress the occurrence of tumour.

## CONCLUSION

Therefore, it can be concluded that the regulation of oncogenic signal vs anti-oncogenic signal should be understood/identified and diagnosed for the future therapy of cancer.

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## CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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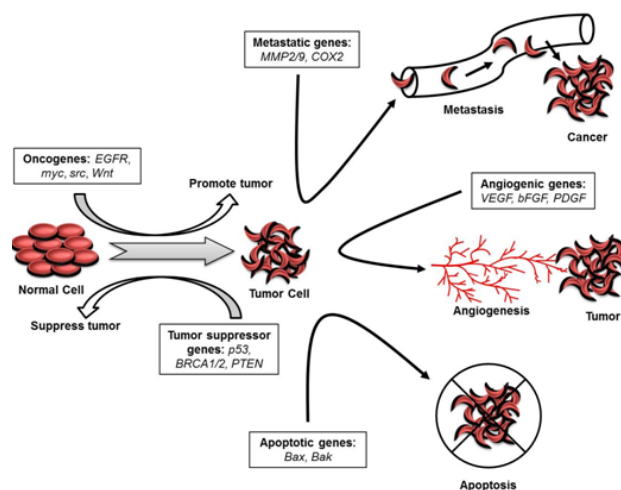


Figure 3 Role of cancer critical genes in Cancer progression.

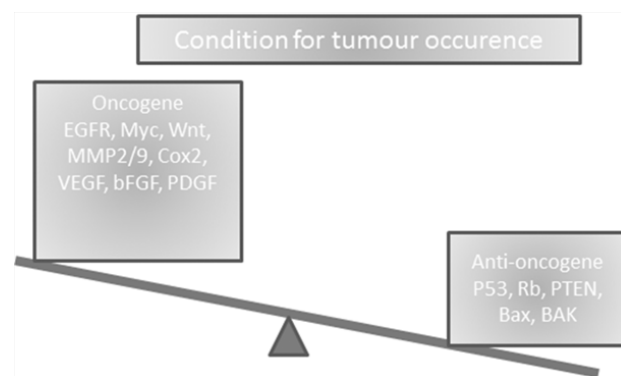


Figure 4 Condition of tumour occurrence; high oncogene and low anti-oncogene.

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