Journal of Scientific and Technical Research
12 (1&2) 2022, 47-54
http://www.publishingindia.com/jstr

Signaling Pathways Associated with Cancer Development and Metastasis

Annesha Das[1], Rishi Anand[1], Vikas Sharma[1], Arun Kumar[1], Anshul Singh[2] and Sandeep Kumar[1*]
[1]School of Pharmacy, Sharda University, Greater Noida, Uttar Pradesh, India
[2]School of Allied Health Sciences, Sharda University, Greater Noida, Uttar Pradesh, India
*Corresponding Author: ph.sandeep@gmail.com

Abstract: Cancer is one of the leading causes of mortality and morbidity worldwide. From decades and decades cancer has been the most undefeated diseases all over the world, despite of clinical research and trials. Cancer term also refers to proliferation of cells. At the time of cancer development, there is a imbalance between tumor suppresser genes and tumor oncogenes. Among the type of cancers, lung and breast cancer are the most common type of cancer worldwide. It further leads for abnormal cell cycle and results in tumor formation. This whole process involves a series of pathways like, Wnt-Beta Catenin pathway, TNF pathway, MAPK pathway, NF-kB pathway, Arf/p53 pathway, intrinsic and extrinsic pathways of apoptosis. This exhaustive review note throughs a lime light on different pathways for the development and progression of cancer. Scientists working in related field may find this article useful. The role of different enzymes and biomolecules in cancer development has been elaborated in the manuscript.

Keywords: Abnormal cell cycle, Biomolecules, Cancer, Different pathways, Proliferation.

I. Introduction

From decades and decades cancer has been the most undefeated diseases all over the world, despite of clinical research and trials. It has been the major causes of death. Data was analyzed by United States of America from 19's all the mortality cause or deaths of cancer cause at specific site due to age, race and sex. Mortality due to age from reports in 1994 was 6% morethan 1970 but decreased by 1% from 1991 to 1994 [1]. The basic process of cancer is almost nearer to each other or we can say similar to each other. Almost around 30 Trillian cells are present in normal or healthy human body which is not dependent on normal cell [2]. Tumor cells are fast growing cells, patients which are infected with cancer sometimes does not show symptoms for which a metastases method have been introduced to identify or detect the circulating tumor cells (CTC) and disseminated tumor cell (DTC) in the peripheral blood and in the bone marrow, which was further classified into three approach such as cytometric, immunological and molecular approach. Peripheral blood approach is more preferred over bone marrow approach for patients suffering from solid tumor which also help in molecular characteristic [3].

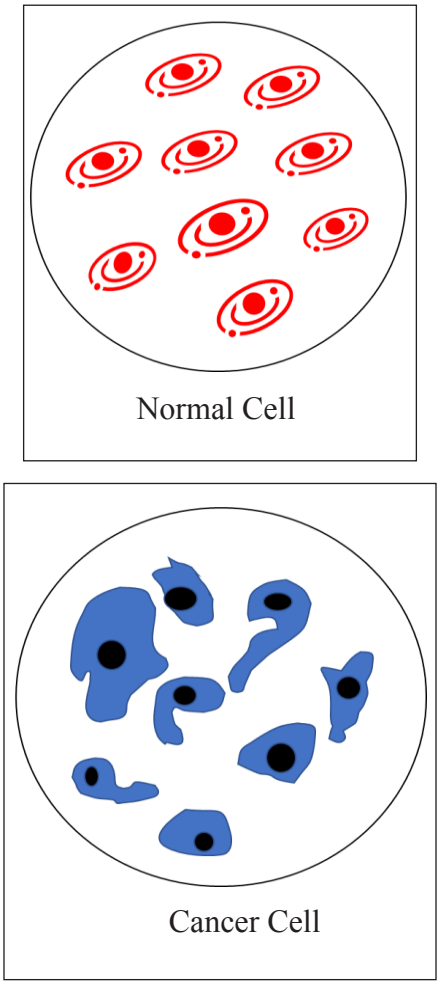

Fig. 1: Showing the Diagrammatic difference Between Normal and Cancer Cell

II. Types of Cancer

A. Breast Cancer

Breast cancer or locally advanced breast cancer is the nowadays the most advanced breast cancer, which is most widely spreaded, it is curable with the mode of surgery, medication and therapies. It is caused by two types either by penetrating the adjusting tissue and another by large loco regional lymph node involvement which can lead to death of the patient [4]. Patients who are detected with early stage of breast cancer are given neoadjustment chemotherapy. In this type of therapy pathologic complete response shows long term survival, but despite of many research and trials pcr in not able to established a link between pcr rate and outcome of the data. Methods used may be the limitation of this unexpected deviation. Definition of pcr has not been established, yet some of the studies add the focal invasive cancer or non-invasive cancer residue as the definition of cancer [5].

In younger women the major cause of death is diagnosis and treatment faced by the patient which cause psychological imbalance thus morbidity occurs [6]. It is one of the most common diseases found in women [7].

According to reports almost 25% of women suffering from cancer are diagnosed with breast cancer, which lead to the fact of mortality rate of 570000 deaths in 2015. Breast cancer is a type of cancer which can easily spread to the vital organs which are also located far away. If this disease is diagnosed at early stage this might lead to the survival of the patient [7].

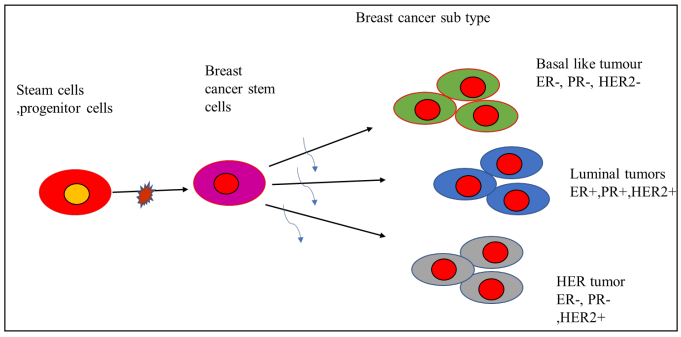

Fig. 2: Diagram Showing the Formation of Cancer Cell in Breast Cancer

B. Lung Cancer

Lung cancer is one of the most complex neoplasm, which are therefore explained for centrally occurring squamous carcinomas in the lungs which added to the small cell lung carcinoma and adenocarcinoma. There are different morphologically from follows as squamous dysplasia, a typical adenomatous hyperplasia and diffuse idiopathic pulmonary neuroendocrine cell hyperplasia, occurs or detected mostly in the lungs of smokers. There are two molecular pathways one for the smoker and another for the non-smokers, the pathways are RAS signalling pathway associated with the smokers and activation of EGFR signalling pathways associated with the non-smokers, found in the histological research of respiratory epithelium [8].

Smoking is a nicotinic addiction, which does not permit the smokers to withdraw smoking. Carcinogen is smoked by tobacco. DNA binding occurs after the tobacco smoked get metabolized which may lead to apoptosis, if the DNA mutation or miscoding continue which is a key gene in the pathway of P53 and RAS leading to genetic instability and mutational damage thus causing cancer [9].

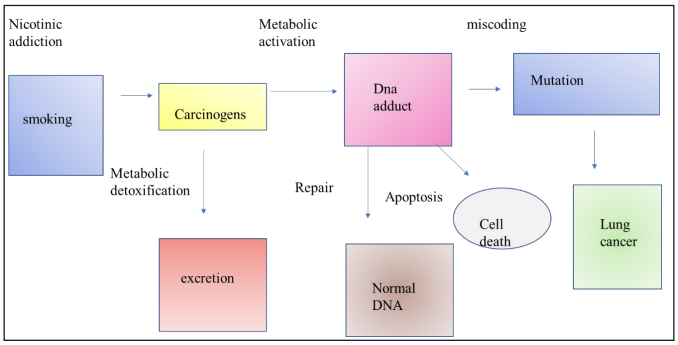

Fig. 3: Diagrammatic Representation for the Formation of Lung Cancer [9]

Lung cancer was at the death end during the early of 20th century but gradually decreases the rate till the need of the century according to the United States of America, but the war for this have not yet came to end. Many of the factors have been identified for lung cancer, such as arsenic nickel random in the workplace and also some factors are associated with the environment such as passive smoking and air pollution. It will remain as usual as inescapable [10].

C. Thyroid Cancer

Thyroid cancer is mostly found in women than in men. In 2015 around 62000 cases were diagnosed in both male and females. There are several subtype of cancer of which differentiated thyroid cancer is most the common of all, treatments effective for this type of thyroid cancer is radioactive iodine. Some of the several sub types of thyroid cancer are medullary and anaplastic. This rare type of thyroid cancer can be treated by physicians, but the drugs are not completely curable [11].

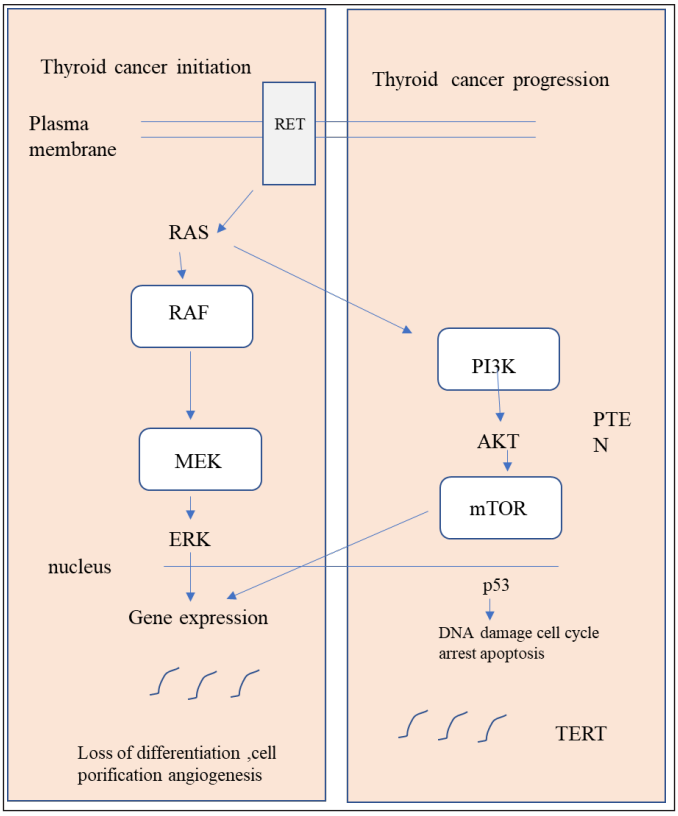

Fig. 4: Showing Thyroid Cancer Progression or Pathway [11]

As per the reports thyroid cancer has been increasing rapidly in past few years and for detecting this type of cancer some methods were used which of these are diagnostic imaging and fine needle biopsy. The guideline provides by the latest American thyroid association for the adult patient related to thyroid cancer dissimilar from the former American thyroid association guidelines. Obesity is one of the factors of thyroid cancer [12]. About 90% of the thyroid cancer shows papillary carcinoma, 5-15% shows follicular carcinoma, the most hardest one is anaplastic carcinoma which shows less than 2% and medium ranges up to 6 months, the next one is medullary carcinoma which shows 5% of the cancer, gene mutation occurring 45%, gene translocation takes up to 15-45% [13].

D. Pancreatic Cancer

Pancreatic cancer is one of the deadliest diseases which cause death to a large rate. The main disadvantage of these type of cancer is they does not show symptoms until the advance stage. Most of the pancreatic cancer arises from pancreatic duct, the four main gene are KRAS, CDKN2A, TP53, SMAD4. Diagnostic method for pancreatic cancer is endoscopic ultrasonography, guided by fine needle method. Surgical method is preferred, after operation chemotherapy is given with gemcitabine and those non-surgical patient are suggested to take FOLFIRINOX and gemcitabine plus nanoparticle albumin bound paclitaxel [14]. Till today the causes of pancreatic cancer are unknown [15] and remained unsolved diseases yet, the patient suffering from the pancreatic cancer eventually form metastases and leads to death. Smoking, age and genetic disorder are some of the factors leading to pancreatic cancer. Advancement in the field of molecular studies leads to fact of mutation occurring of K-Ras oncogene and tumour suppressor gene are also inactivated but diagnosis of the diseases is extremely poor. Treatment for these diseases is sedative, fluorouracil chemoradiation and gemcitabine chemotherapy for locally advanced and metastatic diseases gives sedative effect [16].

E. Cervical Cancer

Cervical cancer is found to be mostly developing in women. Causes of this type of cancer are smoking, exposed to human papillomavirus and immune system dysfunctioning. Patient diagnosed in early stage are mostly cured, though morbidity for long time is usual sometime. After randomised clinical trials patients suffering from stage IB tumours have receive surgeries and radiotherapy although the treatment remain ineffective in many of the cases [17].

F. Prostate Cancer

Prostate cancer is one of the most occurring cancers in men. It may not show symptoms at creation and frequently lead to slothful that may require only active surveillance time to time. This type of cancer id highly seen in elderly men (differs according to age). African American man have shown most aggressive probability of these cancer than white man. Researcher is not able to find an evidence to prevent or cure prostate cancer, however the increasing rate can be lowered by limiting high fat food diet, increasing the intake of fruits and vegetables and performing exercise timely [18]. Prostate cancer is mostly adenocarcinomas which share numerous feathers which corelate with other epithelial cancer such as breast cancer and colon cancer. In view very less research has been invested to find out the molecular pathway for prostate cancer. Type of prostate cancer that can be seen in man of early twenties and fairly in fifties is prostate intraepithelial neoplasia [19].

III. Pathways of Cancer

A. Arf/p53

The pathway regulated by retinoblastoma and p53 are connected by ARF tumor suppressor [20].

Two canonical tumor suppressor cell, retinoblastoma protein and p53 which act negatively in various steps of cell cycle their pursuit are adjusted by products of INK4a/ARF locus, p16INK4a and p19ARF, acts in tumor monitoring. RB phosphorylation by CDKs during G1 phase disturb the alliance with histone deacetylase and transcription factor E2F allows the activities to initiate DNA synthesis. p16INK4a put a stop in E2F activation and inhibit the cell from leaving the G1 phase by disturbing the activity of cyclin D. By unsuitable mitotic signaling the

homothermic factor p53 is induced. Protein stabilizes the activation and accumulation and thus activate apoptosis. Products of p53 reactive gene are p21CIP1 which inhibit the protein cyclin dependent kinase and Mdm2 a negative feedback regulator which end the po53 retaliation. In human p14ARF stabilize and activates p53.6, 7,8,9 thus breaking the cell cycle when response to mitotic signal is disturbed [20].

P16INK4a and p19ARF are encrypted from first part of axons, from there RNA are cut into pieces for sequencing by another part of exon which are convert in two different readings frames, underscoring an unparalleled of genome organization of upper eukaryotes. E2F persuade ARF and biochemically attach the RB and p53 pathway. Some oncoprotein such as MYC, Adenovirus E1A, RAS and v-Abl 12 13 14 15 persuade by ARF highlighting its role in sensing hyperproliferative signals in basic cancer cell. ARF thus has the capability of crucial p53 in tumor observation [20].

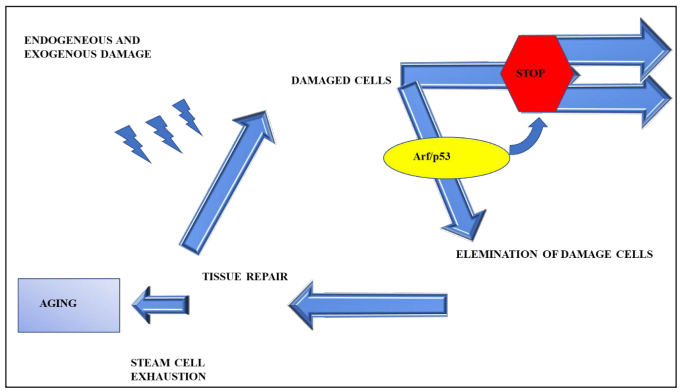

Fig. 5: Showing the Arf/p53 Pathway

B. TNFAlpha Pathway

The superfamily of TNF/TNFR cytokines includes tumors necrosis factor alpha. TNF- participates in inflammation, host defense, and immune system maintenance and homeostasis similarly to other family members. There is a "despair" to this potent cytokine; It is known that, particularly in mid and aged, TNF- is intricate in pathological processes like chronic inflammation, autoimmune disease, and, seemingly against its name, malignant disease. This article will discuss TNF-'s role in the inflammatory network that has an influence on every stage of the malignant process and consider whether TNF- might be a prospective target for cancer therapy [21].

TNF has been linked to a variety of different illnesses. TNF is currently used to treat local new soft tissue sarcomas, metastatic melanomas, and other desirable cancers of any histology in order to prevent limb elimination. It has been shown that TNF- and cytostatic medications work together synergistically in the isolated limb perfusion situation. TNF- interacts with TNFR-1 and TNFR-2, triggering a number of signal transduction pathways and causing TNF- to have a range of impacts. The signaling molecules of TNFR-1 are well known, however the regulation of the signaling is still not completely understood. In addition to these fundamental revelations, laboratory studies over the previous ten years have illuminated TNF-action during tumors therapy [22].

TNF-alpha modulates immune responses to various cells and molecules, the local and vascular attack of tumors, and the damage of tumor vasculature. It also plays a role in a number of physiological and pathologic cellular processes, such as cellular proliferation, differentiation, and death. Due to its integrated functions within various physiologic systems, TNF-alpha could not be used as a single agent therapy for neoplasms. But, extensive research into its variety of cellular pathways has revealed a variety of successive molecules with more certain interactions that may be ideal as prognostic and therapeutic aspects for neoplasms [23].

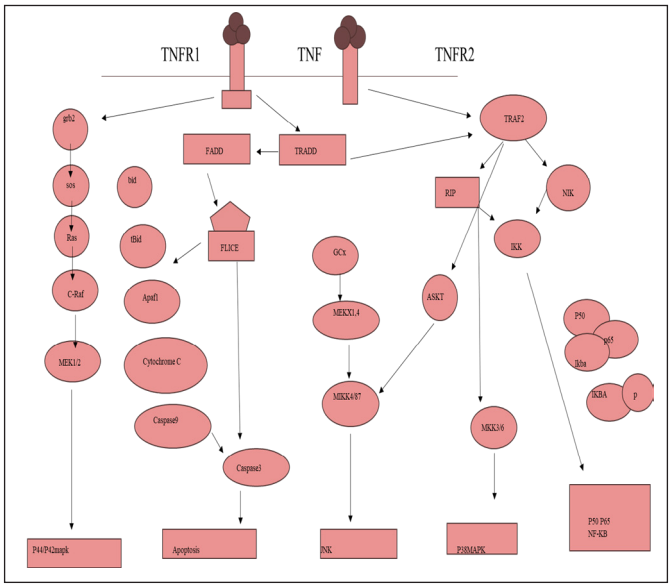

Fig. 6: Diagram Showing the TNF Pathway

C. Wnt Pathway

Through control of tissues' internal stem cells, the Wnt signaling pathway plays a pivotalrole in both tissue enlargement and homeostasis. Aberrant Wnt signaling has been identified as a pivotal factor in the start, continuation, and/or maintenance of numerous malignancies through influencing the actions of cancer stem cells (CSCs). Most people believe that CSCs are to blame for the evolution of the tumors as well as for disease relapse because they naturally resist drugs. New hope for the elimination of CSCs and cancer is offered by the development of therapeutic drugs that specifically target the Wnt signaling pathway. It is critical to determine a method that targets the underactive Wnt pathway in CSCs and is safe enough to not interfere with the normal Wnt pathway [24].

A common feature of many human malignancies is the Wnt signaling pathway. The Wnt pathway has received a lot of research at several molecular levels in associating to the growth

of novel cancer therapies because of its extensive significance in carcinogenesis and progression. Growing evidence from Wnt biology research, which has recently provided a wealth of hints, indicates that the produce Wnt blocker Dick Kopf-linked protein 3 (Dkk-3) and its controllers may represent fascinating therapeutic targets in the most prime human malignancies. From the literature that is accessible, we review what is known about the bioactivity of DKK-3 as a blocker of the Wnt signaling pathway, its participation in different phases of tumor growth, and the genetic and epigenetic factors that impair DKK3 gene function in malignant cells are all described [25].

D. JAK/STAT Pathway

The regulation of crucial cellular functions, including proliferation, capture, survival, inflammation, and immunity, is linked to the Janus Kinase Signal Transducer and Activator of Transcription signaling pathway. The development of metastatic cancer and abnormal JAK/STAT signaling are both influenced by this signaling. The JAK/STAT system must be inhibited in order to increase tumor cell death since STAT proteins are crucial for the growth of cervical cancer. Different STATs are persistently activated in a range of malignancies, include cervical cancer, and their hyperactive may be related with a bad outcome and short overall survival. The oncoproteins E6 and E7, which are necessary for cervical cancer growth, may activate the JAK/STAT pathway [26]. The leading cause of fatality from prostate cancer is the onset of hormone-refractory disease. Higher blood levels of circulating IL-6 are found in patients with hormone-refractory prostate cancer, and studies on cell lines show that the IL-6R/JAK/STAT3 pathway may contribute to the onset of this disease. In the current work, we investigate whether the expression levels of these family members contribute to the establishment of hormone-refractory prostate cancer. Immunohistochemistry was carried out on 50 matched hormone-sensitive and hormone-refractory tumour pairs using the IL-6R, JAK1, STAT3, pSTAT3 Tyr705, and pSTAT3 Ser727 antibodies. When hormone-refractory prostate cancer first developed, shorter time to relapse was correlated with higher expression of the cytoplasmic IL-6 receptor (P=0.0074) [27].

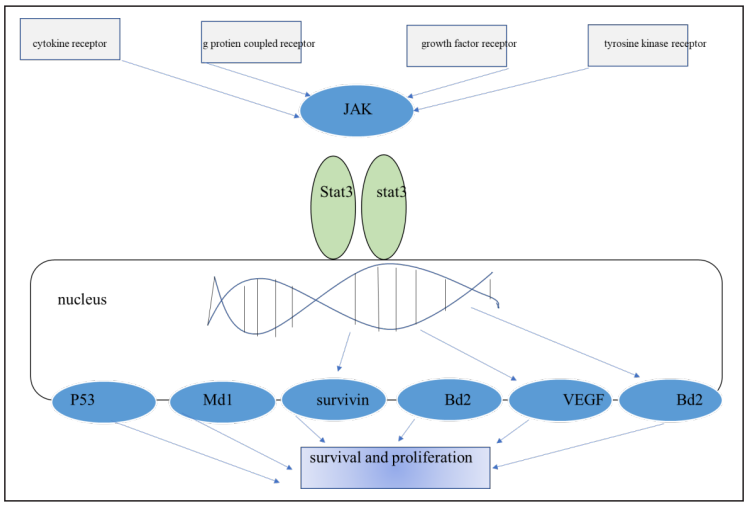

Fig. 7: Showing JAK/STAT Pathway

E. RAS Pathway

The extensive therapeutic aversion of pancreatic cancer, one of the deadliest malignancies in humans, is currently thought to be lead by cancer cells with the ability to self-renew and start offtumors, whether inoperative (cancer stem cells, CSCs), or proliferating (cancer stem-like cells, CSLCs). However, there is still a lot that is unclear about the regulation of pancreatic CSCs/CSLCs. Here, we demonstrate how the K-Ras-JNK axis is essential for maintaining pancreatic CSCs/CSLCs. The ability of pancreatic CSLCs to self-renew and initiate tumors was lost as a result of JNK in vitro inhibition, whether it was brought about by pharmacological or genetic means. Importantly, systemic JNK inhibitor dosing that effectively reduced the CSC/CSLC population by inhibiting JNK in vivo had no obvious impact on the general health state of mice [28]. Muscle differentiation is distinct in the lethal tumour known as embryonic rhabdomyosarcoma (ERMS), which can be caused by the mutational triggering of RAS family members. But the majority of ERMS patients to date have not shown evidence of RAS pathway activation.

In human RMS, activation of the RAS pathway occurs often. Additionally, we developed a novel transgenic co-injection technique to fluorescently mark various tumour cell subpopulations according to the degree of muscle differentiation. The cancer stem cell in zebrafish ERMS using fluorescence activated cell classification, cell transplantation, and limiting dilution analysis. Based on gene expression analyses of this cell type, we hypothesise that the zebrafish RMS cancer stem cell shares self-restoration processes with activated satellite cells [29].

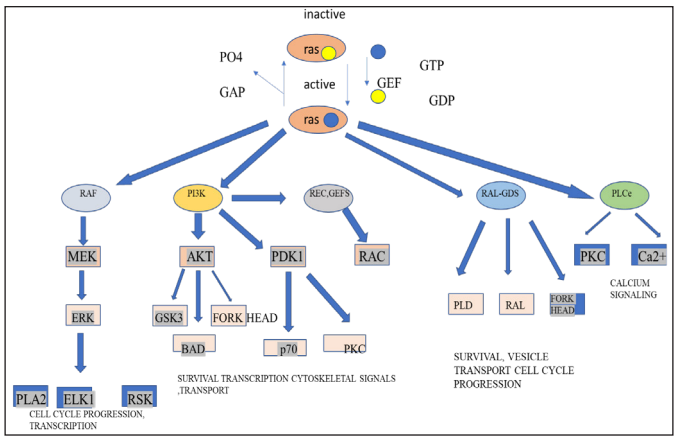

Fig. 8: Showing the RAS Pathway

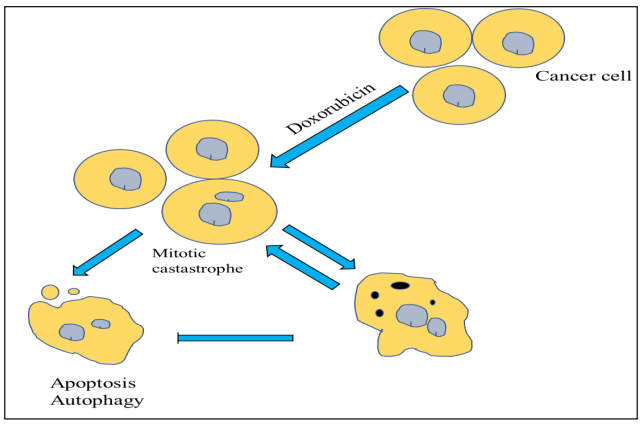

Fig. 9: Showing the Pathway of Cell Apoptosis

F. Cell Apoptosis

The regulation of genes and (epi) genomes, among other cellular and developmental processes, is assisted by chromatin modification. Growing evidence over the past few years has illustrated that incorrect writing, incorrect reading, or incorrect deleting of the modification language lodged in chromatin is a frequent, occasionally early, and pivotal moment across a variety of human cancers, contributing to oncogenesis by inducing changes in epigenetic, transcriptomic, and phenotypic expression. It is becoming progressively clear that cancer-related metabolic disorders and nonhistone mutations also directly influence chromatin reorganization, contributing to the growth of cancer. Deregulation of chromatin modulators and structure based on phase separation is a crucial component of the cancerous process. The various molecular pathways that show a dysregulated chromatin language in cancer [30].

By permitting neoplastic cells to proliferate without cell division, PCD's faults can increase a cell's longevity. Failures in normal apoptosis pathways also promote immune resistance, promote disobedience of cell cycle checkpoints that would ordinarily trigger apoptosis, promote growth factor/hormone-independent cell survival, support anchorage-independent survival during metastasis, and reduce reliance on oxygen and nutrients. These effects all contribute to the development of cancer. The identification of the genes that make up the crucial elements of the cell death pathway has offered new insights into tumour biology and novel approaches to treating cancer [30].

Apoptosis is a coordinated and organized cellular process that takes place under both healthy and unhealthy circumstances. Additionally, it is one of the subjects that cell biologists study the most. Apoptosis' underlying mechanism must be understood because it is essential to the pathophysiology of many diseases. In certain cases, such as in the case of declinatory disorders, the issue is brought on by imprudent apoptosis, but in other cases, insufficient apoptosis is to blame [31].

G. MAPK Pathway

The ERK MAPK pathway is among the most crucial ones for cell proliferation. The MAPK pathways are discovered downstream of a number of growth-factor receptors, counting the epidermal growth factor receptor. A growing amount of research indicates that ERK MAPK overexpression and activation are critical to the development of this malignancy. Colorectal cancer typically displays increase and activation of this receptor. ERK MAPK is a possible target for the disorder's treatment at the molecular level. The ERK MAPK signal-transduction pathway, the implications of its down regulation in colorectal cancer, and its potential as a cancer therapy technique [34].

The mitogen-activated protein kinase/extracellular signal-regulated pathway is initiated by crucial genetic events and/or by the activation of several signaling events that combine at this critical nodal route point. Under normal conditions, this system is tightly regulated by phosphatases and interactions with other pathways, including the protein kinase B/mammalian target of rapamycin (AKT/mTOR) pathway. Current studies suggest that in addition to the more usual pro-oncogenic signal, the MAPK/ERK signaling node can also use as a tumor suppressor. There will be a specific impact depending on the signal's intensity and the environment or tissue where it is aberrantly triggered. A frequent change in the MAPK/ERK pathway component, murine sarcoma viral oncogene homolog B1, has been discovered by genomic profiling of malignancies (BRAF) [35].

The MAPK pathways are essential. Here, we review current searching and hypotheses on the role of MAPK pathways in cancer. The two molecules most typically damaged by malignant mutations in MAPK pathways are Ras and B-Raf in the extracellular signal-regulated kinase pathway. The majority of stress-activated pathways, including p38 and Jun N-terminal kinase, appear to inhibit malignant transformation. Although these signals' integration and balance can change significantly amongst tumors, both factors are crucial to the treatment's effectiveness [36].

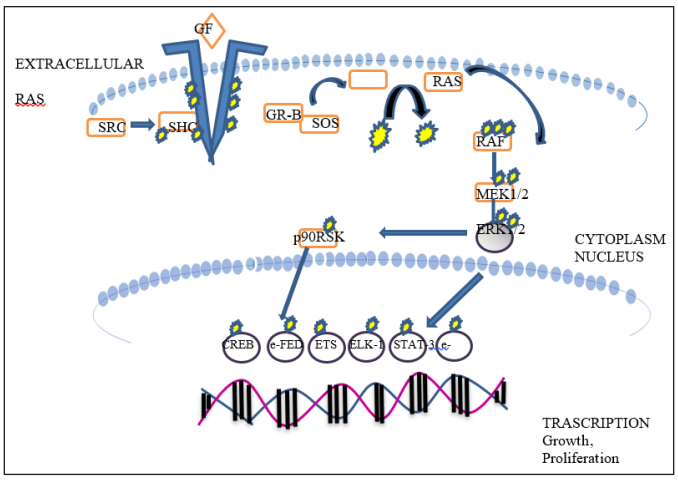

Fig. 10: Showing the MAPK Signaling Pathway

IV. Conclusion

Tumor cells are fast growing cells, patients which are infected with cancer sometimes does not show symptoms for which a metastases method have been introduced to identify or detect the circulating tumor cells (CTC) and disseminated tumor cell (DTC) in the peripheral blood and in the bone marrow, Two canonical tumor suppressor cell, retinoblastoma protein and p53 which act negatively in various steps of cell cycle their undertaking are adjusted by result of INK4a/ARF locus, p16INK4a and p19ARF, acts in tumor monitoring. TNF has been linked to a variety of different illnesses. TNF is currently used to treat locally active soft tissue sarcomas, metastatic melanomas, and other alluring cancers of any histology in order to prevent limb defect. There are different pathways of cancer which plays vital role.

Acknowledgement

Authors are highly thankful to Sharda University. SK wants to pay sincere thanks to Sharda University for providing seed fund SU/SF/2022/07.

Funding: None.

Conflict of Interest: Authors declare no conflict of interest.

References

[1] J. C. Bailar, and H. L. Gornik, "Cancer undefeated," *New England Journal of Medicine,* vol. 336, no. 22, pp. 1569-1574, 1997.

[2] R. A. Weinberg, "How cancer arises," *Scientific American*, vol. 275, no. 3, pp. 62-70. 1996.

[3] K. Pantel, C. Alix-Panabières, and S. Riethdorf, "Cancer micrometastases," *Nature Reviews Clinical Oncology*, vol. 6, no. 6, pp. 339-351, 2009.

[4] D. Simos, M. Clemons, O. M. Ginsburg, and C. Jacobs, "Definition and consequences of locally advanced breast cancer," *Current Opinion in Supportive and Palliative Care*, vol. 8, no. 1, pp. 33-38, 2014.

[5] G. Von Minckwitz, M. Untch, J. U. Blohmer, S. D. Costa, H. Eidtmann, P. A. Fasching, B. Gerber, W. Eiermann, J. Hilfrich, J. Huober, and C. Jackisch, "Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes," *J Clin Oncol*, vol. 30, no. 15, pp. 1796-1804, 2012.

[6] C. Fougner, H. Bergholtz, J. H. Norum, and T. Sørlie, "Redefinition of claudin-low as a breast cancer phenotype," *Nature Communications*, vol. 11, no. 1, pp. 1-11, 2020.

[7] Y. S. Sun, Z. Zhao, Z. N. Yang, F. Xu, H. J. Lu, Z. Y. Zhu, W. Shi, J. Jiang, P. P. Yao, and H. P. Zhu, "Risk factors and preventions of breast cancer," *International Journal of Biological Sciences*, vol. 13, no. 11, p. 1387, 2017.

[8] I. I. Wistuba, and A. F. Gazdar, "Lung cancer preneoplasia," *Annu. Rev. Pathol. Mech. Dis.,* vol. 1, pp. 331-348, 2006.

[9] J. D. Minna, J. A. Roth, and A. F. Gazdar, "Focus on lung cancer," *Cancer Cell*, vol. 1, no. 1, pp. 49-52, 2002.

[10] A. J. Alberg, M. V. Brock, and J. M. Samet, "Epidemiology of lung cancer: Looking to the future," *Journal of Clinical Oncology*, vol. 23, no. 14, pp. 3175-3185, 2005.

[11] M. E. Cabanillas, D. G. McFadden, and C. Durante, "Thyroid cancer," *The Lancet*, vol. 388, no. 10061, pp. 2783-2795, 2016.

[12] C. M. Kitahara, and J. A. Sosa, "The changing incidence of thyroid cancer," *Nature Reviews Endocrinology*, vol. 12, no. 11, pp. 646-653, 2016.

[13] H. Katoh, K. Yamashita, T. Enomoto, and M. Watanabe, "Classification and general considerations of thyroid cancer," *Ann Clin Pathol*, vol. 3, no. 1, p. 1045, 2015.

[14] T. Kamisawa, L. D. Wood, T. Itoi, and K. Takaori, "Pancreatic cancer," *The Lancet*, vol. 388, no. 10039, pp. 73-85, 2016.

[15] M. Hidalgo, "Pancreatic cancer," *New England Journal of Medicine*, vol. 362, no. 17, pp. 1605-1617, 2010.

[16] D. Li, K. Xie, R. Wolff, and J. L. Abbruzzese, "Pancreatic cancer," *The Lancet*, vol. 363, no. 9414, pp. 1049-1057, 2004.

[17] S. E. Waggoner, "Cervical cancer," *The Lancet*, vol. 361, no. 9376, pp. 2217-2225, 2003.

[18] P. Rawla, "Epidemiology of prostate cancer," *World Journal of Oncology*, vol. 10, no. 2, p. 63, 2019.

[19] C. Abate-Shen, and M. M. Shen, "Molecular genetics of prostate cancer," *Genes & Development*, vol. 14, no. 19, pp. 2410-2434, 2000.

[20] C. J. Sherr, and J. D. Weber, "The ARF/p53 pathway," *Current Opinion in Genetics & Development*, vol. 10, no. 1, pp. 94-99, 2000.

[21] F. Balkwill, "TNF-α in promotion and progression of cancer," *Cancer and Metastasis Reviews*, vol. 25, no. 3, pp. 409-416, 2006.

[22] R. van Horssen, T. L. Ten Hagen, and A. M. Eggermont, "TNF-α in cancer treatment: Molecular insights, antitumor effects, and clinical utility," *The Oncologist*, vol. 11, no. 4, pp. 397-408, 2006.

[23] P. M. Sharif, P. Jabbari, S. Razi, M. Keshavarz-Fathi, and N. Rezaei, "Importance of TNF-alpha and its alterations in the development of cancers," *Cytokine*, vol. 130, p. 155066, 2020.

[24] Y. Duchartre, Y. M. Kim, and M. Kahn, "The Wnt signaling pathway in cancer," *Critical Reviews in Oncology/ Hematology*, vol. 99, pp. 141-149, 2016.

[25] J. Veeck, and E. Dahl, "Targeting the Wnt pathway in cancer: The emerging role of Dickkopf-3," *Biochimica et Biophysica Acta (BBA) - Reviews on Cancer*, vol. 1825, no. 1, pp. 18-28, 2012.

[26] A. Gutiérrez-Hoya, and I. Soto-Cruz, "Role of the JAK/ STAT pathway in cervical cancer: Its relationship with HPV E6/E7 oncoproteins," *Cells*, vol. 9, no. 10, p. 2297, 2020.

[27] S. Bose, S. Banerjee, A. Mondal, U. Chakraborty, J. Pumarol, C. R. Croley, and A. Bishayee, "Targeting the JAK/STAT signaling pathway using phytocompounds for cancer prevention and therapy," *Cells*, vol. 9, no. 6, p. 1451, 2020.

[28] M. Okada, K. Shibuya, A. Sato, S. Seino, S. Suzuki, M. Seino, and C. Kitanaka, "Targeting the K-Ras-JNK axis eliminates cancer stem-like cells and prevents pancreatic tumor formation," *Oncotarget*, vol. 5, no. 13, p. 5100, 2014.

[29] D. M. Langenau, M. D. Keefe, N. Y. Storer, J. R. Guyon, J. L. Kutok, X. Le, W. Goessling, D. S. Neuberg, L. M. Kunkel, and L. I. Zon, "Effects of RAS on the genesis of embryonal rhabdomyosarcoma," *Genes & Development*, vol. 21, no. 11, pp. 1382-1395, 2007.

[30] J. C. Reed, "Dysregulation of apoptosis in cancer," *Journal of Clinical Oncology*, vol. 17, no. 9, pp. 2941-2941, 1999.

[31] R. S. Wong, "Apoptosis in cancer: From pathogenesis to treatment," *Journal of Experimental & Clinical Cancer Research*, vol. 30, no. 1, pp. 1-14, 2011.

[32] A. L. Rinkenbaugh, and A. S. Baldwin, "The NF-κB pathway and cancer stem cells," *Cells*, vol. 5, no. 2, p. 16, 2016.

[33] J. I. Inoue, J. Gohda, T. Akiyama, and K. Semba, "NF-κB activation in development and progression of cancer," *Cancer Science*, vol. 98, no. 3, pp. 268-274, 2007.

[34] H. Khan, H. Ullah, P. C. M. F. Castilho, A. S. Gomila, G. D'Onofrio, R. Filosa, F. Wang, S. M. Nabavi, M. Daglia, A. S. Silva, and K. R. Rengasamy, "Targeting NF-κB signaling pathway in cancer by dietary polyphenols," *Critical Reviews in Food Science and Nutrition*, vol. 60, no. 16, pp. 2790-2800, 2020.

[35] J. Y. Fang, and B. C. Richardson, "The MAPK signaling pathways and colorectal cancer," *The Lancet Oncology*, vol. 6, no. 5, pp. 322-327, 2005.

[36] L. Santarpia, S. M. Lippman, and A. K. El-Naggar, "Targeting the MAPK–RAS–RAF signaling pathway in cancer therapy," *Expert Opinion on Therapeutic Targets*, vol. 16, no. 1, pp. 103-119, 2012.