Archives in Cancer Research©
3 (11) 2023 : 001-003 • MINI REVIEW

A multipurpose oncogenic route

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AUTHORS' CONTRIBUTION: (A) Study Design · **(B)** Data Collection . **(C)** Statistical Analysis · **(D)** Data Interpretation · **(E)** Manuscript Preparation · **(F)** Literature Search · **(G)** No Fund Collection

ABSTRACT

Carcinogenesis is defined as unregulated cell development that has the potential to penetrate and disturb important tissue processes. This malignant process includes the emergence of 'unwanted' gene changes that cause normal cells to convert, such as via over activation of pro-oncogenic pathways and inactivation of tumor-suppressive or anti-oncogenic pathways. It is now recognised that the number of main signalling pathways that govern oncogenesis is restricted; hence, blocking these pathways might lead to a cancer cure. However, practical applications of cancer treatments have fallen short of scientific aspirations. Numerous investigations have showed that many oncogenic-signalling elements have dual functions, promoting or suppressing cancer pathogenesis depending on tissue type, cancer stage, gene dosage, and interactions with other participants in carcinogenesis. The intricacy of oncogenic signalling complicates standard cancer therapy and necessitates extreme caution when developing an anticancer medication approach. With the notion of integrated cancer therapy, we suggest future oncology approaches.

Keywords: Oncogenic signaling; Cancer progression; Chemotherapeutic agents; Growth factors; Genetic mutations; Leukemia

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Word count: 1552 **Tables:** 00 **Figures:** 00 **References:** 10

Received: 02.05.2023, Manuscript No. ipacr-23-13685; **Editor assigned:** 04.05.2023, PreQC No. P-13685; **Reviewed:** 18.05.2023, QC No. Q-13685; **Revised:** 23.05.2023, Manuscript No. R-13685; **Published:** 30.05.2023

INTRODUCTION

Oncogenic signalling pathways are important in the genesis and progression of solid tumours as well as haematological malignancies. It is widely understood how these oncogenic signalling pathways work and how critical mutations in these signalling pathways contribute to cancer formation. Oncogenic signalling promotes cancer progression in both solid and haematological tumours by controlling growth, proliferation, cell cycle progression, and apoptosis. Activation of important oncogenic signalling is linked to drug resistance in a variety of malignancies, which is one of the major challenges in effectively treating cancer patients with chemotherapeutic drugs. Too far, numerous inhibitors have been produced to reduce carcinogenesis by targeting critical signalling molecules and mutations in these oncogenic signalling pathways. Cell surface receptors and their corresponding ligands play critical roles in cellular signalling activation, which promotes cancer spread and EMT-like characteristics in cancer cells. Oncogenic signalling mostly operates through the phosphorylation and activation of several transcription factors, controlling the expression of target genes involved in cancer. Depletion or inhibition of key kinases in these oncogenic signalling pathways has been found to limit cancer cell proliferation and induce apoptosis. This review will concentrate on important oncogenic signalling pathways, mutations, and inhibitors in solid tumours and haematological malignancies.

Cancer is a condition in which cells have the ability to divide and expand uncontrolled, generally as a result of genetic changes in certain genes. Over the last decade, advances in DNA sequencing have enabled us to rigorously analyse these genetic alterations, and we now have a better grasp of the processes and signalling pathways that are typically implicated. As more genetic abnormalities become drug-targetable, DNA sequencing is becoming increasingly common in clinical practise. However, there is significant diversity in the genes and pathways affected between tumour types and individual tumour samples, and a thorough knowledge of the genes and pathways altered in all cancer forms is required to uncover possible treatment options and vulnerabilities [1-5].

Several critical signalling pathways, including the RTK/RAS/MAP-Kinase (hence sometimes referred to as RTK-RAS for simplicity) pathway, PI3K/Akt signalling, and others, have been found as often genetically changed in cancer. Members of these pathways and their interactions have been documented in a variety of pathway databases, including Pathway Commons, which aggregates 20 databases, including REACTOME and KEGG. Genes in

important pathways are not altered at the same frequency, with some being often and well-knowingly mutated in cancer while others are only rarely or never altered. The discovery of uncommon changes frequently necessitates a large number of samples. This is complicated by the difficulty of distinguishing between functionally relevant (or "driver") and non-oncogenic "passenger" events, particularly in tumour forms with a high background mutation load. Many mutations, including those found in cancer genes, may have no functional effect in these circumstances. Previous investigations by The Cancer Genome Atlas (TCGA) have gradually mapped out the landscape of changes in signalling pathways. Certain pathways, such as RTK-RAS signalling or the cell cycle pathway, are altered in many different tumour types, whereas others are altered in more specific subsets of malignancies (for example, alterations in the oxidative stress response pathway are strongly associated with squamous histologies). With more than 10,000 samples characterised by TCGA, there is a chance to comprehensively characterise and describe changes within well-known cancer pathways across all tumour types, as well as map out commonalities and variations among pathways. The prevalence of similar genetic traits across histologies has previously been noted, but these studies have usually used a gene-centric, rather than a pathway-centric, approach. Identifying inter- and intra-pathway recurrence, co-occurrence, or mutual exclusivity links among various types of malignancies might aid in elucidating functionally relevant mechanisms of oncogenic pathway modifications that may guide therapy approaches.

The identified genes in the 10 pathways were then examined for recurring changes within and across tumour types in the following ways: Alterations to pathway members were classified as either activating (typically specific recurrent missense mutations, i.e., hotspot mutations, amplifications, or fusions involving oncogenes) or inactivating (truncating mutations, specific recurrent missense or inframe mutations, deletions, fusions, and promoter hypermethylation of tumour suppressor genes). Individual modifications were also examined for two characteristics: statistical recurrence across tumour sample sets and anticipated functional impact. We initially used MutSigCV for mutations and GISTIC 2.0 for copy-number changes to assess statistical recurrence. We then used recurrence across tumour samples at the residue level (linear and 3D mutational hotspots, and prior knowledge about specific variants via the OncoKB knowledge base, which contains information about the oncogenic effects and treatment implications of variants in >400 cancer genes) to identify likely functional variants. The RESET method (see Methods) was used to assess epigenetic silencing of tumour suppressor genes via promoter DNA hypermethylation. The STAR-Fusion, EricScript, and BreakFast algorithms were used to identify gene fusions and structural rearrangements in RNA-Seq data, and potential passenger events were filtered out according on OncoKB annotation. Genes with no indication of recurring or previously known oncogenic changes were deleted from the preliminary pathway templates using this method. Individual route experts or the associated TCGA-PanCanAtlas pathway-specific analytic working groups assessed the resultant curated pathway templates and identified genomic changes for functional significance. Oncogenic and binary genomic alteration matrices are evaluated for pathway member genes and genetic changes [6-10].

CONCLUSION

Although breast and lung cancers are the main causes of mortality in both men and women, prostate cancer is the most frequent cancer in men and has the greatest incidence rate. As a result, if its care is neglected, it may result in certain negative results in patients. Prostate cancer beginning and development are difficult as a multifactorial illness, and their causes have not been well understood, and there is still a long way to go. Although lifestyle, environmental factors, and chemical exposure can all contribute to the development of prostate cancer, genetic abnormalities are as crucial and critical. As a heterogeneous malignant tumour, a single gene is not engaged in regulating prostate cancer growth. As a result, some of the most significant genes with high dysregulation should be chosen for novel therapies in prostate cancer treatment. STAT3 signalling has been involved in controlling carcinogenesis in several malignancies, among other molecular pathways. STAT3 is overexpressed in brain tumours, gastrointestinal tumours, urological malignancies, and haematological cancers. As a result, it is a prospective target for cancer therapy, with the current review focusing on the function of STAT3 signalling in prostate cancer.

First and foremost, it is important to comprehend the interplay of STAT3 signalling with other pathways in controlling the proliferation and metastasis of prostate tumour cells. According to research, inhibiting STAT3 signalling inhibits the proliferation and invasion of prostate cancer cells. In prostate tumour cells, STAT3 knockdown causes death and cell cycle arrest at the G2/M phase. Although studies have clearly proven the significance of STAT3 signalling in raising the proliferation rate of prostate tumour cells, future research should focus on the role of STAT3 signalling in regulating DNA damage repair, which is important in cancer cell radiation response. Increasing evidence suggests that activating STAT3 signalling promotes prostate tumour cell invasion and metastasis, which is primarily mediated by the EMT process, as shown by in vitro tests on cell lines and xenograft models. As a result, it is proposed that STAT3 signalling be inhibited in order to reduce prostate cancer growth and invasion. Silencing STAT3 signalling improves medication resistance in prostate cancer, and future research should concentrate on the function of STAT3 signalling in inducing radio-resistance. Because prostate cancer is a malignant and potentially fatal illness in males, there has been an endeavour to develop novel therapies and anti-cancer drugs. Capz, -elemonic acid, ligustilide, and resveratrol are beneficial in inhibiting STAT3 signalling and slowing the growth of prostate tumour cells. In addition to chemotherapy and radiation, researchers have

increasingly concentrated on employing immunotherapy for various tumours, including prostate cancer. However, in prostate cancer, stimulation of STAT3 signalling and overexpression of its downstream target PD-L1 can result in immune evasion. There are two major constraints that need be addressed in future research. First, the researchers are pre-clinical, and it is highly recommended that further effort be made in translating existing findings into clinic. Furthermore, small compounds and phytochemicals have been utilised to reduce STAT3 signalling, and it is proposed that nanostructures be studied for their involvement in reducing STAT3 signalling and slowing prostate cancer growth.

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