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Assessment of cellular signaling pathways in cancer: Targeting aberrant kinases and phosphatases for personalized therapy

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Abstract. Cancer is a group of diseases where cell proliferation is uncontrolled leading to formation of tumors which can spread to other parts of the body in a process called metastasis. With a mortality of about ten million deaths each year, cancer is responsible for one in six deaths which makes it one of the leading health problems worldwide. Because of this it is necessary for scientists to research cancer thoroughly to stop this problem as soon as possible. Cellular signaling pathways regulate cell proliferation, depending on the ligand that binds to cells it can lead to cell growth or apoptosis. So if a mutation happens in one of these pathways it can lead to serious problems such as the constant activation of the pathway causing uncontrolled cell growth and thus, cancer. In this review, I will focus on the aberrant kinases and phosphatases describing their pathways with detail and seeing how to target these mutations using combinatorial therapy with signal-transduction inhibitors to try to stop the pathogenesis of cancer. So far, there is no known cure for cancer and only some treatments in phase III are available. Trying to cure cancer is very complex, especially in cancer treatment as each patient may have genetic variations, the molecular profile of the tumor, and other unique biological characteristics, herein, personalized therapy based on different patients' situation to increase treatment effectiveness while minimizing side effects. In this review, we intend to elucidate the significance of targeting aberrant kinases and phosphatases in the pathogenesis of cancer.

Keywords: cellular signaling pathways, kinases, phosphatases, combinatorial therapy.

1. Introduction

Cancer is characterized by uncontrolled cell growth and the ability of cells to evade normal regulatory mechanisms while cell signaling pathways are a major contributor to these processes. Some of these pathways are the Hedgehog pathway, the Wnt pathway, the Notch pathway and the NF-kB pathway. However, the most frequently mutated ones are the PI3K/Akt/mTOR pathway and the Ras/MAPK pathway. The JAK/STAT pathway is also important as it can also activate the PI3K/Akt/mTOR pathway and the Ras/MAPK pathway. Plus, the JAK/STAT pathway also mediates inflammation in cells which is associated with 15 to 25% of cancer cases [1]. In the normal condition, these pathways are functionally well, but cancer happens when these pathways are dysregulated or unbalanced.

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1.1. PI3K/Akt/mTOR pathway

This pathway is mainly activated when a growth factor or a hormone such as insulin attaches to a receptor tyrosine kinase (RTK), causing the receptor to dimerise and to autophosphorylate. Phosphatidylinositol 3-kinases (PI3K) can be activated by insulin receptor substrate 1 (IRS-1) binding to the phosphorylated dimer, by binding to a GTP (guanosine triphosphate) bound Ras molecule or it can bind directly to the phosphorylated receptor. This active PI3K phosphorylates phosphatidylinositol 4,5-bisphosphate (PIP2) into phosphatidylinositol 3,4,5-trisphosphate (PIP3) in the inner cellular membrane. PIP3 concentration increase leads to the recruitment of phosphoinositide-dependent kinase-1 (PDK1) which directly phosphorylates Akt at Thr308 to activate Akt or it can indirectly activate mTOR (mammalian or mechanistic target of rapamycin) Complex 2 to phosphorylate Akt at Ser473. Akt activation leads to cell proliferation and survival, and inhibits apoptosis.

1.2. Ras/MAPK pathway

This pathway is also activated by mitogens, specifically when TGF-α (transforming growth factor) binds to an epidermal growth factor receptor (EGFR) leading to the dimerisation and self-phosphorylation of the receptor. Next, Grb2 (growth factor receptor-bound protein 2) binds to one of the phosphate groups and SOS (son of sevenless) binds to Grb2 causing inactive GDP (guanosine diphosphate) bound Ras to turn into its active form GTP bound Ras initiating the cascade by activating B-Raf (MAPKKK) which phosphorylates MEK 1/2 (mitogen activated protein kinase kinase/MAPKK) which then activates ERK 1/2 (extracellular signal regulated kinases/MAPK) leading to the activation of transcription factors of the AP-1 (activator protein) family, mainly fos and jun. As a consequence, growth factors, cyclins and cytokines are expressed and cell proliferation happens. To inactivate this cascade, GAP (GTPase activating or accelerating proteins) attaches to Ras and hydrolyses GTP into GDP.

1.3. JAK/STAT pathway

The Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway is activated when cytokines such as GM-CSF (granulocyte macrophage colony stimulating factor) or hormones like thrombopoietin or interferons and interleukins attach to a cytokine receptor. JAK molecules are recruited by the active receptor and phosphorylate tyrosine residues in the receptor allowing the Sh2 (Src homology 2) domain of STAT molecules to be able to bind. Then, JAK phosphorylates STAT which makes STAT dissociate from the receptor and dimerise through their Sh2 domains. Finally, STAT enters the nucleus and promotes transcription of many target genes such as MYC which is an oncogene involved in cell cycle progression and apoptosis. Activation of this pathway leads to hematopoietic cells proliferating and epithelial cells forming cell adhesions. JAK2, a member of the Janus kinase family, can activate the Ras/MAPK pathway by activating a protein complex made by SH2-domain containing transforming protein (SHC), growth factor receptor-bound protein (Grb), and SOS. Plus, it can activate the PI3K/Akt/mTOR pathway through IRS1/2.

2. Role of aberrant kinases and phosphatases in cancer

Kinases are enzymes that phosphorylate proteins and phosphatases dephosphorylate proteins. These enzymes are important in cellular signaling pathways as the addition and removal of phosphate groups cause conformational changes in the enzymes which can activate or inhibit it. Kinases and phosphatases are vital for the signal transduction cascades so if one of them is aberrantly activated the cascade will not be able to stop and it can lead to uncontrolled cell proliferation.

2.1. Mutations in the PI3K/Akt/mTOR pathway

Aberrant Akt promotes tumor growth and accelerates metastasis. For example, overexpression of Akt lead to a higher probability of phosphorylation of Twist1 or phosphorylation of Girdin which promotes cancer metastasis. Also, overexpression of Akt2 (an isoform of Akt) can promote breast cancer cell migration and mutant Akt1 can promote melanoma metastasis. Activation of Akt 1/2 insertion-deletion mutations (indels) can lead to breast cancer, prostate cancer, clear cell renal cancer, etc. Furthermore,

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Akt1 E17K point mutation can cause breast cancer, ovarian cancer, endometrial carcinoma, meningioma, etc [2].

PTEN is a phosphatase enzyme which can stop the PI3K/Akt/mTOR pathway by dephosphorylation of PIP3 into PIP2 so inactivation of this enzyme has been seen in solid tumors, leukemias, and myeloproliferative neoplasias [3]. PTEN mutations or deficiencies are commonly found in prostate cancer, breast cancer, endometrial cancer, glioblastoma multiforme, thyroid cancer, etc [2]. Furthermore, monoallelic mutations (mutations in one allele) in PTEN have been observed in gliomas (75%), breast (40-50%), prostate (42%), lung (37%), and colon (20%) cancers and biallelic mutations (mutations in both alleles) in PTEN have been seen in endometrial (50%), glioblastoma (30%), prostate (10%) and breast (5%) cancers [4].

Another common mutation in this pathway happens in mTOR which is a serine/threonine kinase. Abnormally activated mTOR promotes tumor cells growth and metastasis [5]. mTOR mutations are present in 10.4% of melanoma, 6% of clear-cell renal cell carcinoma, 7.5% of lung adenocarcinomas, 5% of endometrial carcinomas, and 4% of colorectal carcinomas [6].

2.2. Mutations in the Ras/MAPK pathway

Mutated Ras is unable to hydrolyse GTP back to GDP to stop the pathway so the Ras/MAPK pathway is permanently activated which can lead to carcinogenesis. There are 3 types of Ras proteins: H, N and K. In bladder tumors H-Ras is most commonly mutated, in colon and pancreas cancer K-Ras is most commonly mutated and N-Ras mutation usually leads to hematopoietic tumors. Approximately 30% of human cancers occur due to activating point mutations in RAS genes, those of which 85% happen in K-Ras [4].

There are 3 Raf proteins: A, B and C. However, the most important is the point mutation in B-Raf V600E which leads to a permanently active B-Raf. This mutation can be found in 8% of human carcinomas, most commonly in 41% of melanomas, 45% of papillary thyroid cancer and 14% of colon cancer. C-Raf mutations rarely happen and A-Raf mutations have not been described yet [4].

Moreover, MEK 1/2 mutations have been detected in very low frequencies in human cancers such as melanomas (3%) and colon (2%) carcinomas and no activating mutations of ERK 1/2 have been found in human cancers [4].

2.3. Mutations in the JAK/STAT pathway

JAK2 is the most commonly mutated JAK protein. Many chromosomal translocations in JAK2 have been discovered, for example, NF-E2.JAK2 causes myelodysplastic syndrome (MDS). Moreover, another important gene mutation of JAK2 is V617F which results in a JAK2 protein that is constitutively activated. This mutation is present in more than 80% of polycythaemia vera (PV) patients and 50% of thrombocythemia cancer pathogenesis [7,8]. JAK 1/3 mutations were found in a study in 49% of patients suffering from T-cell prolymphocytic leukemia [9]. Furthermore, JAK1 G871E mutation has been seen in uterine leiomyosarcomas, JAK1 S703I mutation results in inflammatory adenoma and leukemia, and aberrant JAK3 leads to acute megakaryoblastic myeloid leukemia [10].

3. Personalized therapy

Targeting the aberrant kinases and phosphatases listed previously might help us to find a cure for some specific types of cancer. However, as each cancer is so complex and the drugs affect each person differently it is very difficult to find one specific drug for each cancer. Because of this combinatorial therapy is needed to target multiple pathways at once depending on the biomarkers of the patient.

In the PI3K/Akt/mTOR pathway, Akt is one of the most promising targets as it leads to so many pathways. There are two Akt inhibitors which are already in phase III clinical trials: Capivasertib and Ipatasertib, that can be used in combination with other drugs to target specific types of cancer. For example, a combination of Capivasertib with Paclitaxel can be used to treat triple negative breast cancer (TNBC) and a combination of Ipatasertib with Abiraterone and Prednisolone can be used to treat metastatic prostate cancer [2].

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The mTOR signaling pathway is one of the primary targets for finding a cure for the pathogenesis of cancer as it is mutated and active in most of the human cancers. Some anticancer drugs that target the mTOR kinase specifically were already approved in some countries. For example, Temsirolimus and Everolimus which are used to treat kidney or breast cancer. Moreover, for the patients who acquired resistance to mTOR targeted drugs, a new mTOR inhibitor was developed called Rapalink-1 which showed to reduce the tumor size significantly[5].

Dual PI3K/mTOR inhibitors have been observed to be more effective than mTOR inhibitors alone, but they are still at an early stage of trials so additional research is needed. Some examples of these inhibitors are: Dactolisib, Apitolisib and Gedatolisib which have shown significant anticancer effects in several tumors [11].

For the Ras/MAPK pathway there are still no specific inhibitors of Ras developed, however, there are specific inhibitors for EGFR, B-Raf and MEK 1/2. For example, for EGFR some anticancer drugs which are currently being developed are Gefitinib or Erlotinib, for B-Raf Vemurafenib and for MEK 1/2 mutations PD98059 and U0126 have shown in vitro antiproliferative effects [11]. Other MEK 1/2 are being tested in phase I clinical trials such as AZD8330. For Raf, Sorafenib is currently the best inhibitor as studies have demonstrated Sorafenib to be a potent aberrant B-Raf V600E inhibitor in vitro [12]. However, several phase II/III trials with Sorafenib have failed to achieve any significant improvement, but trials combining Sorafenib with other agents are still being evaluated.

In the case of the JAK/STAT pathway, there are already several approved JAK inhibitors. For example, Ruxolitinib which inhibits JAK1 and JAK2 can be used to treat primary and secondary myelofibrosis but with intermediate or high risk [13], or Lestaurtinib, which is still in clinical trials, against JAK2 for acute myeloid leukemia (AML) [14]. These drugs inhibit the JAK activity blocking cytokines signalling which are responsible for cell growth. Many more JAK inhibitors are being developed in vitro, with mice and in different phases, for instance, AT9283 which targets JAK2 and JAK3 to treat multiple myeloma and this drug seems to not produce any toxicity at the phase II stage, or NVP-BSK805 which has only been used in mice but can treat PV efficaciously by targeting all 3 Janus kinases [10].

4. Clinical implications and challenges

Even though so many anticancer drugs seem to have been approved and so many are being developed, there are still some challenges for the cure of cancer. Firstly, one of the main problems is patient heterogeneity, each person has a different body with different physiological responses to certain drugs, plus, the age and race and genetic predisposition are all factors needed to be taken into account when administering a drug. Therefore, personalized therapy by targeting kinase and phosphatases are beneficial for specific types of cancer.

Furthermore, the biggest problems are drug resistance and the possible side effects of the drugs. For example, inhibiting the Akt pathway can disrupt the glucose uptake of some tissues leading to hyperglycemia which is one of the common side effects of Akt inhibitors, and also with MEK inhibitors such as CI-1040 diarrhea, asthenia, rash, nausea, and vomiting are frequent toxicities [12]. Fedratinib, a JAK inhibitor which reached phase III trials, was discarded even though it was effective against myelofibrosis as it would cause encephalopathy in patients. A similar example is Pacritinib, which was a JAK2 inhibitor that was also in the third stage of the clinical trials, and it was discontinued due to patients dying regardless of the drug's potency against myelofibrosis [10]. These are the reasons why developing a cure to carcinogenesis is such an arduous task, as even if you can elaborate a successful anticancer drug it can be cancelled due to its side effects or because the tumors become resistant. To countermeasure acquired resistance to the drugs proper combinational therapy should be developed.

5. .Conclusion

Due to the complexity of cancer pathogenesis and the numerous cellular signaling pathways that can be involved in just one type of cancer, developing anticancer drugs is a very complicated challenge.

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Personalised combinatorial therapy seems to be the best way to target mutant kinases and phosphatases in signal transduction pathways in order to increase the chances of survival of cancer patients.

The PI3K/Akt/mTOR pathway and the Ras/MAPK pathway are very frequently mutated in cancer and they are probably the most studied pathways. They are essential, not only for cell survival and growth, but also for lipid, protein and glycogen synthesis, transcription of vital genes and for autophagy of malignant cells. Other pathways like the JAK/STAT pathway are also connected to the PI3K/Akt/mTOR pathway and the Ras/MAPK pathway so inhibiting only those two pathways is not enough.

Kinases and phosphatases are vital enzymes in these pathways as they are involved and regulate most of the signal transduction and amplification. Because of this, mutations in these proteins are recurring in the pathogenesis of cancer which means that the inhibition of specific kinases and phosphatases can stop the cellular signaling pathways in the carcinogenic cells in order to detain tumor growth. Obviously, there are other options to cancer such as epigenetics, RNAi (RNA interference) pathway or targeting the receptors of the signal transduction pathways to try to stop tumorigenesis, but focusing in specific kinases and phosphatases is definitely another effective way with a great future prospect.

Targeting various pathways at the same time with drugs specific to certain biomarkers using combinatorial therapy might be a way to prevent problems like drug resistance. But the toxicity of the drugs needs to be carefully evaluated before giving the drug to any patient because of their heterogeneity. This field definitely needs to be studied and researched much more and more longitudinal clinical trials should be done to develop effective anticancer drugs.

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