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The Importance and Effect of Protein Kinase on Cancer Formation and Growth

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Protein kinases are a large and important group of protein enzymes that are in the human genome. These proteins are responsible for phosphorylation of target proteins. Phosphorylation is the addition of a phosphate group to a protein in order to cause a functional, conformational change in the way the target protein acts. The reason why protein kinases are of importance in medicine and science is because of the role that these enzymes play in the development and growth of cancerous tumors. This research is relevant to millions of people who suffer from, or know someone who suffers from any type of cancer. In this paper, protein kinases and allosteric regulation of enzymes will be reviewed in order to better understand why these enzymes are so important in regards to cancer. Phosphorylation is a critical step in the growth of cancer cells. Utilizing this information, there has been a large area of research concerning protein kinase inhibitors. These drugs can be made in order to inhibit the phosphorylation process, and eventually kill the pathways that facilitate the growth of cancerous cells. However, there is still much research that needs to be done in order to fully understand the role that protein kinase enzymes play in the process of cancer.

Introduction

Protein kinase research is critical for the development of drugs that can inhibit the growth of cancerous cells. First, there must be extensive research on protein kinases in order to accomplish the task of curing cancer. Three papers will be reviewed during the course of this paper. The first paper deals with the research of protein kinases, and their quantity in non-small cell lung cancer cells (NSCLC). W.N. William, among others, wrote a paper research paper titled, *The Impact of Phosphorylated AMP-activated Protein Kinase Expression on Lung Cancer Survival*, concerning a specific protein kinase termed, phosphorylated AMP-activated protein kinase (pAMPK). This research team investigated the amount of pAMPK in lung cancer cells of patients that differed in their smoking pasts. They took cancer cell samples from patients that had never smoked in their life, those that had quit smoking, and from those patients who are current smokers. The tissue samples were then surgically taken out of the patients, and the pAMPK was stained in order for the research team to decipher the results. The NSCLC patients' pAMPK results were correlated with their survival year after year.

The second paper that will be reviewed is titled, *The Energy Landscape Analysis of Cancer Mutations in Protein Kinases.* Anshuman Dixit and Gennady M. Verkhivker co-wrote and researched protein kinase activation with a focus on allosteric regulation in cancer cells. Allosteric regulation is one of the four main regulatory processes that enzymes undergo. Specifically, allosteric regulation is when either an activator or inhibitor molecule attaches to the enzyme at a site away from the active site, which causes a conformational change in the shape of the enzyme. This corresponding shape change alters an active site, and influences what can and cannot bind to the altered active site. These regulators are involved in physiological feedback mechanisms, among many other tasks. Specifically, Dixit, and Verkhivker studied allosteric protein kinase activation. One of the main points that Dixit and Verkhivker discovered is that activated cancer mutations might affect the thermodynamic equilibrium between different kinase states. The allosteric altering that occurs when cancerous cells reproduce their mutated genes causes this equilibrium change. This research is intended to ultimately find out why tumors form, and consequently, why they rapidly undergo uncontrollable divisions. These scientists have concurred that whenever a protein atypically activates, it creates a strong source or tendency for that protein to end up causing tumor mutations.

The third paper that is being referenced to in this review concerns protein kinases and their mutations that cause cancer. The paper, written by Gosul, Kochut, and Kannan is titled, *ProKinO: An Ontology for Integrative Analysis of Protein Kinases In Cancer.* In this peer-reviewed article, the researchers have found mutational profiles of protein kinase genes. They found these profiles from numerous different types of cancer. These scientists utilize the ProKinO process, which stands for protein kinase-specific ontology. This system contains many features of protein kinases, such as vocabulary, hierarchy, sequence, structure, and function of protein kinases. The main benefits of using the ProKinO are to be able to rapidly discover information that is related to a specific protein kinase (Gosul 1). In addition to discovering information in a timelier manner, researchers can analyze integrative data that they would not otherwise be able to do as easily. All three referenced papers concern protein kinases and the fact that they undergo some sort of genetic altering in cancer.

Recent Progress

Over the past couple of years, there has been a lot of research and experiments regarding protein kinase. Protein kinases have been found to have an ever-increasing role in the development and growth of cancer. Protein kinase inhibitors have been synthesized in recent years as drugs that inhibit the phosphorylation process that kinase enzymes are known for. Phosphorylation is a necessary process that many biochemical reactions, such as cellular respiration, must use in order to survive. Recent progress in the field of oncology has shown that tumors depend on phosphorylation in some cancers. This knowledge of how cancer spreads, combined with the knowledge of protein kinases, allows researchers to be able to create drugs that can hopefully stop or slow down aggressive cancers. There has been recent research suggesting that AMP protein kinase is involved in the formation of cancer. Everyday there is new research and progress concerning the formation of cancer, and how these cells are able to continue to divide. In the article concerning pAMPK, they state the recent studies that they have performed show that pAMPK can be used as a tumor suppressor, and that this same kinase can help protect normal cells as well.

Discussion

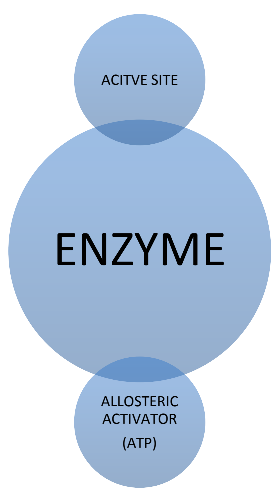
In the first article that was discussed, *The Impact of Phosphorylated AMP-activated Protein Kinase Expression on Lung Cancer Survival*, the researchers took cancerous lung tissue from three different types of patients. The patients in the study were either non-smokers, smokers, or former smokers. . The researchers in the article found a strong correlation between non-smokers and high pAMPK levels in the cancerous cells. In addition to non-smokers having a significantly higher level of pAMPK, the data also showed that this same group of patients had significantly higher survival rates over the course of seven years. The study made some more conclusions from the research of AMPK, "A number of studies in the literature have suggested that AMPK is a key cellular fuel sensor and may couple energy metabolism with cell proliferation" (William 81). In the first article, the authors state that there are some limitations, and some unanswered questions. One of the main limitations mentioned was, "Also, in this preliminary study, we did not examine the expression levels of downstream effectors of AMPK, which could provide further evidence (or lack thereof) of the functional status of pAMPK" (William 82). The authors go on to say that this is the first study of its kind, referencing the study of pAMPK and lung cancer survival. This article was very well written, and the research team produced results that can very well help other researchers and medical professionals in the future. This article leaves unanswered questions, such as how pAMPK works in animals. There needs to be more studies and research in order to figure out how to use this information to stop the spread of lung cancer, and other cancers. Overall, the study and the article are very significant in cancer research, but as with all other research, there needs to be more research conducted.

In the second reviewed article, "*The Energy Landscape Analysis of Cancer Mutations in Protein Kinases",* concludes that whenever a protein is mutated, or abnormally activated, that it is likely that this protein can cause a cancer to form. In addition to these findings, the authors found that, "The presented study has demonstrated that activation cancer mutations may affect the thermodynamic equilibrium between kinase states by allosterically altering the distribution of locally frustrated sites and increasing the local frustration in the inactive form, while eliminating locally frustrated sites and restoring structural rigidity of the active form" (Dixit 1). This article is helpful in understanding the dangerous effects that occur whenever a protein undergoes a mutation. Questions still remain concerning exactly how, or what exactly causes mutations to protein kinases. More research is needed across the board in order to be able to fully understand what causes the root of cancer.

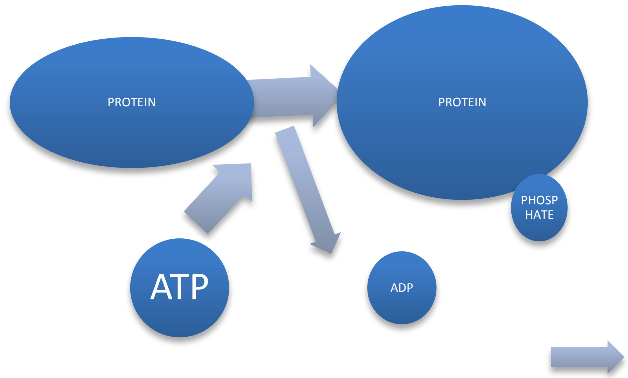
The third reviewed article titled, "*ProKinO: An Ontology for Integrative Analysis of Protein Kinases In Cancer*". The whole point of this article is to demonstrate ProKinO, which is protein kinase-specific ontology, as previously mentioned. ProKinO gives researches a plethora of information that is specific to protein kinase, and its relationship with ontology. Protein kinase, as concluded in this article, controls signaling pathways. These pathways include, but are not limited to cell growth and survival. One of the challenges of integrative analysis that the authors had to deal with is, “disparate nature of protein kinase data sources and data formats” (Gosal 1). As similar with all other experiments, more information must be found on this subject in order for scientists to get a better understanding of how these proteins work, and how they are associated with cancer causing mutations.

The research of proteins and the way they interact in every bodily interaction, including diseases such as cancer, is critical to medicine. There needs to be more research in the area of protein kinases and how they help or cause cancer. However, there also needs to be more research in factors other than proteins, such as diet and environmental effects, which can help prevent or treat cancer. This research is important for the medical industry, pharmaceutical industry, and every human being on earth. There has been great headway in this area in recent years, and there will be even more great advancements in the coming years.

FIGURES



THIS FIGURE SHOWS AN ALLOSTERIC ENZYME, AND IT IS DEPICTING HOW THE ACTIVATOR/INHIBITOR WILL BIND AWAY FROM THE ACTIVE SITE.



THIS DIAGRAM DEPICTS A NORMAL PROTEIN ON THE LEFT THAT GETS PHOSPHORYLATED BY THE BIG ARROW (PROTEIN KINASE). ATP GOES INTO THE REACTION, AND ADP COMES OUT ON THE OTHER SIDE. THE SMALL SPHERE ON THE RIGHT PROTEIN IS THE PHOSPHATE GROUP THAT HAS BEEN ATTACHED TO THE PHOSHORYLATED PROTEIN.

References

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