Reprogramming Metabolism In Cancer

Cellular metabolism is a recent and main focus in the study of the development of cancer. Glycolysis is responsible for converting glucose to pyruvate and, in aerobic conditions, the pyruvate will go to the mitochondria so it can be oxidized through pyruvate dehydrogenase and tricarboxylic acid (TCA) cycle enzymes. Intermediates produced from the TCA cycle are essential to create macromolecular precursors which act as metabolites for glycolysis and other pathways, in order to promote proliferation. However, they can also be utilized as fuel for various metabolic functions of cancer cells and the vast range of potential fuels is extremely advantageous for proliferating tumors. Scientists are exploring various mutations and their connection to tumor progression and the pathophysiology of the disease. One category of reprogrammed metabolic activities is known as transforming activities. These metabolic activities, under oncogenic control, are directly linked to cell transformation and are caused by somatic enzyme mutations in a recurring sequence and/or inherited through cancer predisposition syndromes. There are only a few transforming metabolic activities known at the moment and the most studied of these mutations are: isocitrate dehydrogenases-1 and -2 (IDH1, IDH2) genes, succinate dehydrogenase (SDH) complex and fumarate hydratase (FH) (Vander Heiden, Matthew G, and Ralph J DeBerardinis, 2017). These mutations have been shown to have significant consequences on cellular metabolism and it appears as though an individual with these mutations has a significantly increased risk for developing cancer. The goal of exploring these mutations is to direct future research to the focus of reprogrammed metabolic activities and hopefully improve patient care through a better understanding the impact these mutations have on cellular mechanisms.

Mutations of IDH1 and IDH2 occur in several different cancer types and have been studied extensively, especially through gliomas. A mutation in these genes converts ?-ketoglutarate (?KG) to (D)-2-hydroxyglutarate (D-2HG) and the D-2HG is found at very high levels in IDH mutant tumors. These increased levels is important because it causes a disruption of ?KG-dependent dioxygenases which can lead to severe consequences in the cell such as the preventing epigenetic enzymes from properly regulating methylation of histones and DNA that subsequently affects gene expression (Vander Heiden, Matthew G, and Ralph J DeBerardinis, 2017). Scientists are interested in the mutations of the genes and their prevalence related to gliomas. One laboratory produced a genomewide mutational analysis of glioblastomas which found that a correlation to the mutations of IDH1 that were found in a specific class of tumors and was most likely seen in tumors evolving from lower-grade gliomas (secondary glioblastomas) (Yan, Hai, et al., 2009). They took this a step further by using cultured glioma cells transfected with these mutations to identify the exact mutation in the IDH1 and IDH2 genes. They concluded that a mutation in amino acid 132 of IDH1 was present in over 70% of astrocytomas, oligodendrogliomas and glioblastomas rising from a lower-grade glioma. They also stated that those tumors that did not possess a mutation in IDH1 were often likely to have a mutation in amino acid 172 of the IDH2 (Yan, Hai, et al., 2009). These findings are significant because Yan’s laboratory has been able to clearly identify a mutation largely presented in common tumor types and has also paved the way to preventing these mutations and improving patient care.

The next mutations being studied in cancer metabolism is those of the succinate

dehydrogenase complex (SDH) and fumarate hydratase (FH). These enzymes are key contributors to reactions within the TCA cycle and both act as tumor suppressors. These tumors have a similar consequence as the IDH1 and IDH2 genes as they produce high levels of succinate and/or fumarate which affect gene expression through interference of the ?KG-dependent dioxygenases (Vander Heiden, Matthew G, and Ralph J DeBerardinis, 2017). Succinate and fumarate are the substrates for SDH and FH and have been shown to control signaling pathways in metabolism. Even though SDH and FH are known to be 'housekeeping genes' with various bioenergetic functions, it has been shown that mutations in these genes, infact, can be linked to tumor progression and cancer. Mutations identified within the subunits B, C or D of SDH lead to the growth and spread of paraganglioma or phaeochromocytoma while mutations in FH lead to leiomyoma, leiomyosarcoma or renal cell carcinoma (King, A, et al., 2006). Although, it is greatly significant that mutations in SDH and FH, as well as IDH1 and IDH2, have been linked to the formation of very specific cancers; there are still many aspects scientists are puzzled by and continue to study. As mentioned before,the signalling pathway maintained and regulated by succinate or fumarate appears to cause tumor growth in cells with a deficiency of SDH or FH, however, this pathway does not show how or why different forms of cancer develop in one protein versus another. Although, not much is known as of why those specific cancers mentioned form from these mutations, a significant amount of evidence has been presented to show that the inhibition of ?-KG-dependent histone and DNA demethylases causes a change in gene expression and inadvertently has tumorigenic effects.

The mutations of IDH1 and IDH2, SDH and FH have all been shown to affect ?-ketoglutarate which plays crucial roles in various metabolic and cellular pathways. One of the affected pathways is the inhibition of multiple ?-KG-dependent dioxygenases, including histone demethylases, which causes alterations of histones throughout the genome and DNA methylation and therefore likely plays a key role in tumorigenesis (Xiao, Mengtao, et al., 2012). When mutated IDH1 and IDH2 are expressed in tumors , 2-HG is produced and competes with ?-KG for binding of ?-KG-dependent dioxygenases which induces inhibition of these enzymes. This evidence supports the fact that hypermethylation is commonly shown in patients with glioma due to mutations of IDH1 and AML due to mutations of IDH1 and IDH2. Following this, fumarate and succinate have very similar structural characteristics to that of ?-KG and 2-HG, including the same acetate end and oxygen atoms at carbon-5. These specific structural components are utilized by both ?-KG and 2-HG in order to competitively inhibit ?-KG-dependent dioxygenases as well as prolyl hydroxylases (PHDs)(Xiao, Mengtao, et al., 2012). This study has been able to show that IHD1 and IDH2, SDH and FH through different mechanisms are all liked to the inhibition of ?-KG-dependent dioxygenases which causes epigenetic modifications which over time will lead to tumor progression.

Although each of the four studies mentioned all contribute to the evidence that reprogramming of cellular metabolism can be linked to tumorigenesis and the development of cancer; they still approach the issue through individualistic and unique methods. Vander Heiden, Matthew G, and Ralph J DeBerardinis focus on the this issue of metabolism and cancer biology as a whole. They mention different proposed reprogrammed metabolic activities such as transforming, enabling and neutral activities and how each category activity together sets the cancer cell up for viable conditions for tumor growth. They go on to also discuss the products of metabolism, such as ATP and NADPH and if they are limiting for proliferation. This laboratory is interested in many different aspects of the regulation of metabolism as many different variables would have to be studied in order to find an appropriate treatment for the disease. One issue they bring to light which can be applied to the other reviews mentioned is the question of what determines

how different tumors use metabolism. This is better presented by Yan, Hai, et al. and King, A, et al. as these laboratories focus on the specificity of cancers that form from each mutation. Yan, Hai, et al. are interested in the study of IDH1 and IDH2 mutations found in gliomas at such a high percentage and what pathway causes the mutation to lead to the most common types such as astrocytomas, oligodendrogliomas, and ependymomas. Following this, King, A, et al. instead focuses on the study of SDH and FH mutations and the evidence supporting the formation of paraganglioma or phaeochromocytoma for SDH mutations and leiomyoma, leiomyosarcoma or renal cell carcinoma for FH mutations. These two laboratories focus on different mutations, however, they both are looking for observations that explain why each mutation is responsible for such a specific cancer type and evidence as to what mechanisms and pathways allow the formation of these types of tumors versus any other forms. Lastly, Xiao, Mengtao, et al. concentrates in depth on how these mutations may influence alterations in gene expression, which the previous reviews began to predict but failed to support through their research and experimentation. This laboratory proposed how mutations in IDH1 and IDH2, as well as SDH and FH, went on to inhibit ?-KG-dependent dioxygenases which causes alterations in histones and inactivation of DNA methylation and ultimately causes changes in gene expression which lead to tumor growth and development of certain cancers. They recognized the common mechanisms shared by the metabolic tumor suppressor genes IDH, FH, and SDH when mutations were present. They concluded with a proposal to control regulation of metabolites and their metabolic enzymes in order to potentially provide a new therapy for treatment of different cancers. Overall these articles were very similar with overlapping ideas, however, they appeared to build off of one another and each provided unique information about what would have to be considered in the future of cancer biology if changing the levels of metabolic intermediates were to become a new main focus for treatment.

In conclusion, cellular metabolism is a very complex pathway which produces many by-products and intermediates. Over the last decade, many scientists have become interested in a few specific mutations that have been found to be highly present in different types of cancer. These findings have fueled an interest in the ability to target these mutations and discover how the mutation affects a change in gene expression through inhibition of ?-KG-dependent dioxygenases. One unique approach scientists are taking is to regulate the transcription by changing/controlling the levels of metabolic intermediates produced, such as fumarate and succinate, which might be affecting gene expression through epigenetic modifications. I am very intrigued by the idea scientists have derived to control metabolic intermediate levels within the human body and look forward to reading on about what methods and techniques will be utilized in order to perform this treatment.