Obesity: GO Term enrichment

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***Abstract* - Obesity is a disorder which involves having excess amounts of body fat. Obesity is defined by behavioral, environmental and genetic factors that are difficult to control when it comes to dieting. A body mass index (BMI) between 25 and 29.9 is an indication of a person carry excess weight. Generally, doctors suggest that a person whose BMI is 30 or greater is considered to have Obesity. In the US alone, there are more than 3 million cases of obesity per year.**

Keywords - Diet, fat, high blood pressure, nutrition, sedentary, and physical activity.

I. Introduction

Obesity is a disorder in which excess body fat accumulates to a certain degree, and results in a reduced life expectancy and increased health problems. Obesity is caused by a combination of genetic, behavioral, and environmental factors. Child obesity is becoming a health problem in countries, developed and underdeveloped alike. Child obesity increases the likelihood of certain diseases, such as Gallbladder disease, type 2 diabetes and hypertension. The genetic and environmental factors associated with obesity have been investigated with great depth, but certain key molecular mechanisms involved in obesity have remained to be identified.

Previous studies have determined certain pathological mechanisms associated with obesity. According to Li, Ling Et al., 2017, one study indicated that body fat and weight were inversely associated with 25-hydroxyvitamin D levels and volumetric dilution may explain for the low vitamin D levels in obese individuals. In addition, leptin-melanocortin signaling has been identified as a key pathway in regulating food intake and body weight. Mutation of ligands or receptors in the leptin-melanocortin pathway may cause obesity. Furthermore, two previous studies indicated that variation in the fat mass and obesity-associated gene was associated with childhood obesity and severe adult obesity (C, Dina Et al, 2007). Very few articles have reported the genes or pathways of childhood obesity alone. As a result, further identification of significant genes and/or pathways associated with child obesity need to be done.

II. Factors

Genetic changes in human populations occur too slowly to be the sole reason for the obesity epidemic. Nonetheless, the variation in how people respond to an environment that promotes a sedentary lifestyle and ease of access to high-calorie foods suggests that genes do in fact play a role in the development of obesity. Although not as greatly as environmental contribution, genetic contribution to obesity has been proved by various research. Genes give the body directions for responding to changes in its surroundings.

Studies have found variants in several genes that may contribute to obesity by way of increasing hunger and food intake. The hormone ghrelin plays an important role in ingestion behavior. It also affects the release of growth hormones and how the body accumulates fat. The activity of the FTO gene is said to impact a person's chances of having obesity because it affects the amounts of ghrelin a person has. It is very rare that a clear pattern of inherited obesity within a family is caused by a specific variant of a

single gene. Most obesity, however, probably results from complex interactions among multiple genes and environmental factors which remain unknown.

Environmental factors are one of, if not the biggest factors that contribute to obesity. It is as simple as thinking about how environmental factors affect your everyday lifestyle; what you do, wear, eat, drink and who you interact with. Food being advertised on television, the ease of access to fast food restaurants in any given neighborhood, the amount of time you have to make a meal, and the kinds of physical activity you chose to engage in, are all environmental factors that contribute to obesity.

III. Pathways related to Obesity

Apelin signaling pathway:

Apelin is an endogenous peptide, belonging to the family of adipokines, capable of binding the apelin receptor (APJ). Apelin and APJ are widely expressed in various tissues and organ systems. They are involved in many physiological processes such as angiogenesis, body fluid homeostasis, energy metabolism regulation and cell proliferation. Similarly, this ligand receptor couple is also involved in several pathologies which include obesity, diabetes, cancer and cardiovascular disease.

Thermogenesis:

Thermogenesis, the production of heat energy is the neutrally-regulated metabolic function of brown adipose tissue (BAT). In brown and beige adipose tissue thermogenesis is mainly controlled by norepinephrine, and contributes to the maintenance of body temperature during exposure to the cold and to the elevated core temperature during several behavioral states, including wakefulness (Morrison Et al, 2014). Thermogenesis is essential for warm-blooded animals, in that it ensures normal cellular and physiological function under conditions of environmental challenge. The mitochondrial uncoupling protein 1 (UCP1) is responsible for the process in which chemical energy is converted into heat in the adipocytes. Activation of the adipocytes leads to an increase in calorie consumption and is expected to improve overweight conditions, providing a potential strategy for treating obesity and its related metabolic disorders.

Insulin resistance:

Insulin resistance syndrome, also known as metabolic syndrome is a condition where cells become resistant to the effects of insulin, resulting in elevated levels of glucose in the blood. It is often found in people with health disorders, including obesity, type 2 diabetes mellitus, and non-alcoholic fatty liver disease. The National institute of Diabetes and Digestive and Kidney Diseases have claimed multiple causes for insulin resistance, a few of which are: (1) increased phosphorylation of IRS (insulin receptor substrate) protein through serine/threonine kinases, such as JNK1 and IKKB, and protein kinase C, (2) decreased activation of signaling molecules including PI3K and AKT, and (3) an increase in activity of phosphatases including PTPs, PTEN, and PP2A. People who are at risk of developing Insulin resistance are among those who are 45 or older, obese or overweight, and have high blood pressure and abnormal cholesterol levels.

IV. Work to be done

There has been extensive research done on obesity, with regards to the factors surrounding it, genes and proteins involved, and how to prevent it. One focus that I noticed a lot was the need to do more research to determine whether there are significant genes and/or pathways associated with child obesity in particular.

V. Methods

For the gathering of information, I used a combination of simple and intermediate techniques. I used the most basic form of text mining, using the find feature (ctrl-f) of pdf readers and webpages, to look for terms related to obesity and genes related to obesity, which helped me select the papers that I found. I searched the NIH site for papers related to obesity, as this site proves more efficient than your typical google search. I read a few papers and articles, and while reading I highlighted important areas that I wanted to include in my paper that I felt

gave more than your typical synopsis of obesity. In addition to that, I used the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway tool to identify pathways related to obesity. Furthermore, I used the Princeton GO term finder tool to identify biological processes and molecular functions based on the genes that I found.

VI. Results

Genes/Gene products	**OMIM #**
MC4R	155541
POMC	609734
LEP	614962
LEPR	614963
Sdc 1,3	186355,186357
CART	602606
GHRL	605353
GHSR	601898
BDNF	113505
NR0B2	604630
ADRBs	109690, 109691
ENPP1	173335
PYY	600781
SIM1	603128

Table 1: Obesity related genes.

Gene Symbol	**Role**
ADIPOQ	Produced by fat cells, and promotes energy expenditure.
FTO	Promotes food intake.
LEP	Produced by fat cells.
LEPR	When bound by leptin, inhibits appetite.
PCSK1	Regulates insulin biosynthesis.
PPARG	Stimulates lipid uptake and development of fat tissue.
INSIG2	Regulation of cholesterol and fatty acid synthesis.

Table 2: Select genes, and their roles in energy balance.

Process	**P-value**
regulation of appetite	4.06e-11
feeding behavior	6.12e-09
response to nutrient levels	1.19e-07
hormone secretion	1.87e-07
response to extracellular stimulus	2.11e-07
regulation of hormone levels	3.07e-07
response to insulin	1.93e-06

Table 3: Biological processes related to Obesity.

Molecular function	**P-value**
hormone activity	6.99e-08
receptor ligand activity	7.61e-06
receptor regulator activity	1.10e-05
signaling receptor binding	2.68e-05
neuropeptide hormone activity	0.00016

Table 4: Molecular functions related to Obesity.

Pathways	**Description**
Insulin resistance	a condition where cells become resistant to the effects of insulin.
Apelin signaling pathway	Apelin is an endogenous peptide capable of binding the apelin receptor and is implicated in process like energy metabolism regulation.
Adipocytokine signaling pathway	Increased adipocyte volume and number are positively correlated with leptin production. Leptin being an important regulator of energy intake.
Non-alcoholic fatty liver disease	Caused by the induction of insulin resistance.

Table 5: Biological Pathways related to Obesity

VII. Conclusion

As a result of this review, there is plenty to walk away with. I not only became familiarized with the factors that contribute to obesity, but also how it increases the risks for more serious conditions and diseases. Furthermore, i've become acquainted with genes, and pathways that obesity is associated with. I already had knowledge on some of the things that can be done to prevent obesity prior to this review, because it is such a hot topic when it comes to human health. The most difficult part of this review was determining what needed to be studied more in regards to obesity. One thing I wanted to come across but did not find was whether dominant or recessive inheritance of obesity can occur.

VIII. References

[1] Li, Ling et al. “Identification of key genes and pathways associated with obesity in children” Experimental and therapeutic medicine vol. 14,2 (2017): 1065-1073.

[2] C, Dina et al. Variation in FTO contributes to childhood obesity and severe adult obesity. Nat Genet. 2007;39:724–726.

[3] “Adult Obesity Causes & Consequences | Overweight & Obesity | CDC.” Centers for Disease Control and Prevention, Centers for Disease Control and Prevention,www.cdc.gov/obesity/adult/causes.html.

[4] “Insulin Resistance & Prediabetes.” National Institute of Diabetes and Digestive and Kidney Diseases, U.S. Department of Health and Human Services, 1 May 2018, www.niddk.nih.gov/health-information/diabetes/overview/what-is-diabetes/prediabetes-insulin-resistance.

[5] Wysocka, Marta B et al. “The Role of Apelin in Cardiovascular Diseases, Obesity and Cancer” Frontiers in physiology vol. 9 557. 23 May. 2018, doi:10.3389/fphys.2018.00557 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5974344

[6] Morrison, Shaun F et al. “Central neural regulation of brown adipose tissue thermogenesis and energy expenditure” Cell metabolism vol. 19,5 (2014): 741-756.

Obesity and angiogenesis

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***Abstract* - Angiogenesis, the formation of new blood vessels, plays critical roles in the human physiology, which range from fetal growth to tissue repair, and the female reproductive cycle. Contrary to this, imbalanced angiogenesis can result in vascular insufficiency and vascular overgrowth (retinopathies, hemangiomas, and vascularized tumors). The balance between pro-angiogenic and antiangiogenic growth factors tightly controls angiogenesis. Obesity on the other hand, is a disorder which involves having excess amounts of body fat. Obesity is defined by behavioral, environmental and genetic factors that are difficult to control when it comes to dieting. Generally, doctors suggest that a person whose BMI is 30 or greater is considered to have Obesity. In the US alone, there are more than 3 million cases of obesity per year. We seek to identify pathways that are common in both and the reason for the intersection.**

Keywords - Diet, fat, high blood pressure, sedentary, blood vessel, cancer, and angiogenesis.

I. Introduction

Obesity is a disorder in which excess body fat accumulates to a certain degree, and results in a reduced life expectancy and increased health problems. Obesity is caused by a combination of genetic, behavioral, and environmental factors. Child obesity is becoming a health problem in countries, developed and underdeveloped alike. Child obesity increases the likelihood of certain diseases, such as Gallbladder disease, type 2 diabetes and hypertension.

Angiogenesis, the word angio meaning blood vessel and genesis meaning creation, is the creation of new blood vessels. Angiogenesis is a crucial process, which occurs during health, as well as disease. The formation of new tissues involves the formation of new blood vessels. When new tissue is formed, it is essential that is has blood supply for its growth and livelihood.

II. Pathways related to Obesity and Angiogenesis

Apelin signaling pathway:

Apelin is an endogenous peptide, belonging to the family of adipokines, capable of binding the apelin receptor (APJ). Apelin and APJ are widely expressed in various tissues and organ systems. They are involved in many physiological processes such as angiogenesis, body fluid homeostasis, energy metabolism regulation and cell proliferation. Similarly, this ligand receptor couple is also involved in several pathologies which include obesity, diabetes, cancer and cardiovascular disease.

Thermogenesis:

Thermogenesis, the production of heat energy is the neutrally-regulated metabolic function of brown adipose tissue (BAT). In brown and beige adipose tissue thermogenesis is mainly controlled by norepinephrine, and contributes to the maintenance of body temperature during exposure to the cold and to the elevated core temperature during several behavioral states, including wakefulness (Morrison Et al, 2014). Thermogenesis is essential for warm-blooded animals, in that it ensures normal cellular and physiological function under conditions of environmental challenge. The mitochondrial uncoupling protein 1 (UCP1) is responsible for the process in which chemical energy is converted into

heat in the adipocytes. Activation of the adipocytes leads to an increase in calorie consumption and is expected to improve overweight conditions, providing a potential strategy for treating obesity and its related metabolic disorders.

Cancer:

Tumor growth and metastasis depend on angiogenesis. In the absence of vascular support, tumors may become necrotic or even apoptotic. Neovascularization, including tumor angiogenesis, is basically a four-step process. First, the basement membrane in tissues is injured locally, resulting in immediate destruction and hypoxia. Second, endothelial cells activated by angiogenic factors migrate. Third, endothelial cells proliferate and stabilize. Fourth, angiogenic factors continue to influence the angiogenic process, thus leading to the progression of cancer. (Nishida Et al, 2006).

According to Fukumura, D. Et al, various studies have shown that more cancers are linked to obesity than previously described. Currently, obesity and being overweight are well-established major risk factors for cancer, accounting for roughly a 40% increase in the incidence of certain cancers. In particular, an association between obesity and increased risk of gallbladder cancer, gastric cancer, cervical cancer, and prostate cancer has been described. Furthermore, a number of large-scale studies have demonstrated that obesity leads to an increase in not only incidence but also cancer-related mortality.

III. Work to be done

There has been research conducted with respect to factors, genes, causes, and implications revolving around obesity and angiogenesis on an individual basis. More work can be done to find whether antiangiogenic factors can result in a decrease of the possibility of becoming obese. The underlying reason for this concern is because adipocytes play a role in both angiogenesis and obesity, and it has been shown that an increase in adipocyte volume is correlated with leptin production. In addition, leptin is said to be an important regulator of energy intake, which greatly affects the chances of becoming obese.

IV. Methods

For the gathering of information, I used a combination of simple and intermediate techniques. I used the most basic form of text mining, using the find feature (ctrl-f) of pdf readers and webpages, to look for terms related to obesity and angiogenesis, and genes related to obesity and angiogenesis, which helped me select the papers that I found. I searched the NIH site for papers that mentioned things related to both angiogenesis and obesity, be it pathways, genes, gene products etc., as this site proves more efficient than your typical google search. In addition to that, I used the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway tool to identify pathways related to obesity and angiogenesis in my previous papers. With those pathway results, I discussed the ones where an intersection occured between angiogenesis and obesity.

V. Results

Gene/Gene products	**Role**
Angiopoietin 1	Induces EC proliferation and produced by adipose tissue.
VEGF	Produced by adipose tissue and Induces EC proliferation.
LEP	Produced by fat cells.
LEPR	When bound by leptin, inhibits appetite.
IL-6	Produced by adipose tissue
HGF	Produced by adipose tissue and stimulates angiogenesis.
TGF-β	Produced by adipose tissue and induces angiogenesis

Table 1: Genes related to both Obesity and angiogenesis.

Pathways	Description
Adipocytokine signaling pathway	Increased adipocyte volume and number are positively correlated with leptin production. Leptin being an important regulator of energy intake.
Apelin signaling pathway	Apelin and APJ are involved in both angiogenesis and obesity.
Cancer	There exists links between cancer and obesity. Growth of the vascular network is important for the spread of cancer tissue.
adipogenesis	Angiogenesis is a key feature of expanding adipose tissues in obesity.

Table 2: Biological Pathways related to both obesity and angiogenesis.

VI. Conclusion

As a result of this review, there is plenty to walk away with. I not only became familiarized with the factors that contribute to obesity and angiogenesis, but also the role each factor plays in the biological processes. Furthermore, i've identified genes, and pathways that obesity and angiogenesis are both associated with. The most difficult part of this review was determining what needed to be studied more in regards to obesity.

VII. References

[1] Li, Ling et al. “Identification of key genes and pathways associated with obesity in children” Experimental and therapeutic medicine vol. 14,2 (2017): 1065-1073.

[2] Nishida, N., Yano, H., Nishida, T., Kamura, T., & Kojiro, M. (2006). Angiogenesis in cancer. Vascular health and risk management, 2(3), 213-9.

[3] “Adult Obesity Causes & Consequences | Overweight & Obesity | CDC.” Centers for Disease Control and Prevention, Centers for Disease Control and Prevention, www.cdc.gov/obesity/adult/causes.html.

[4] Wysocka, Marta B et al. “The Role of Apelin in Cardiovascular Diseases, Obesity and Cancer” Frontiers in physiology vol. 9 557. 23 May. 2018, doi:10.3389/fphys.2018.00557 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5974344

[5] Morrison, Shaun F et al. “Central neural regulation of brown adipose tissue thermogenesis and energy expenditure” Cell metabolism vol. 19,5 (2014): 741-756.

[6] Fukumura, D., Incio, J., Shankaraiah, R. C., & Jain, R. K. (2016). Obesity and Cancer: An Angiogenic and Inflammatory Link. Microcirculation (New York, N.Y. : 1994), 23(3), 191-206.