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Gestational Diabetes Mellitus and Cancer Risk in Pediatrics: A Molecular Pathway and Future Approach

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Abstract

Gestational Diabetes Mellitus (GDM) is a condition that affects the physiology of the mother and fetus during pregnancy. In addition, it has been shown that it also plays a role in the occurrence and progression of pediatric cancer. Epigenetic changes are one of the risk factors that affect pediatric cancer. Moreover, hyperinsulinemia and hyperglycemia are among the conditions that can play a role in childhood cancer due to GDM. In many cases, inflammatory factors activate the NF-κB pathway and lead to inflammation. Furthermore, inhibition of apoptosis inducing factors causes the emergence and proliferation of cancer cells. Also, PI3K/AKT, mTOR, STAT/NF-kB pathways are among the most important pathways involved in the pathogenesis of pediatric cancer. Epigenetic changes, hyperinsulinemia, and hypoglycemia can increase the probability of cancer in children by changing the expression of some genes and signaling pathways. Identifying these pathways can help in the design of treatment strategies and lead to the prevention of cancer and increase the survival of patients.

Key Words: Cancer, Gestational Diabetes Mellitus, Mechanism, Pediatrics.

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1- INTRODUCTION

The incidence of cancer in children is an issue becoming more and more important nowadays (1). Pregnancy conditions and physiological factors of the mother during pregnancy can have a great impact on the incidence of cancer in children. Studies have shown that Gestational Diabetes Mellitus (GDM) increases the risk of cancer in pediatric cases. GDM in mothers can disrupt physiological processes as well as biological processes (2, 3). Although genetic changes and mutations have been shown to be the cause of cancer in children in most of the previous studies, physiological disorders during the mother's pregnancy, among other things, can affect the health of the fetus (4).

Recent studies have shown that many mothers with GDM are obese during pregnancy. Patient's Obesity can disrupt inflammatory reactions and produce inflammatory mediators such as cytokines in placental cells (2, 5). The exact mechanism of pediatric cancer pathogenesis has not been determined, however, it has been shown that some factors can affect the expression and function of genes during pregnancy and lead to the occurrence of cancer in childhood (6). The exact mechanism of these processes is not well understood, so we aimed to investigate it for the first time in this study.

1-1. Epigenetic changes in GDM and risk of cancer

GDM is a type of diabetes that occurs during pregnancy and is associated with an increased risk of cancer in pediatric cases (7). One possible mechanism for this increased risk is through epigenetics, which refers to changes in gene expression without changes in DNA sequences (7). GDM in the mother has been shown to alter epigenetic symptoms in genes involved in cell division and differentiation, which may lead to the development of pediatric cancers (7). One of the epigenetic changes studied in this area is DNA methylation (7).

Insulin-like Growth Factors (IGFs) play an important role in cell growth, proliferation and survival. Epigenetic changes in genes involved in IGF signaling, such as IGF2 and IGFR2, have been observed in GDM and pediatric cancer samples. Increased expression of IGF2 leads to an increase in miR-483 levels and an increase in cell growth and cancer in pediatrics. On the other hand, increased IGF2 gene expression has a dual effect on the expression level of miR-675 in some situations with upregulation, and in some cases by downregulation, plays the role of tumor inducer which is caused by increasing the activity of the signaling pathway IGF2 (8).

In addition, DNA methylation changes can also play a role in the development of pediatric cancer among the children of the mothers with GDM. Hypermethylation of promoter regions leads to the suppression of IGF2 gene and decreased its expression; on the other hand, hypomethylation of DNA leads to an increase in IGF2 expression and increased tumor growth. Therefore, epigenetic changes caused by GDM can lead to impaired regulation of IGF pathways, which may increase abnormal cell growth and increase the risk of pediatric cancer (8).

miR-125b directly suppresses TP53 gene and increases NOTCH signaling pathway activity, thereby reducing the inhibitory effect on tumor cell growth. On the other hand, miR-182 interferes with the DNA repair process by inhibiting breast cancer gene 1 (BRCA1), a gene expression leading to an increase in PIK3/AKT/MTOR signaling pathway. Hypermethylation of BRCA1 and TP53 promoter leads to quenching of this gene, genetic instability, impaired DNA repair, and induction of cancer in pediatric cases.

Therefore, epigenetic changes associated with GDM can affect the expression of tumor suppressor genes such as TP53 and BRCA1, which are essential for maintaining genomic stability and preventing cancer growth. Hypermethylation of promoter regions in these genes can lead to increased resistance to chemotherapy drugs in addition to increased cancer risk (9).

The level of miR-17-92 increases with increased expression of MYC. This microRNA is known as oncomiR and induces cancer in children of mothers with GDM. Increased expression of this gene by increasing mTOR signaling pathway leads to induction of tumor cell growth (10, 11). On the other hand, hypermethylation of promoter regions of tumor suppressor genes such as p16INK4A and p14ARF which are important regulators of cell growth and survival occurs in MYC expression disorder and leads to induction of cancer in these pediatric cases (10). So epigenetic changes can also affect the activation of oncogenes, such as MYC, which are involved in cell proliferation and tumor formation (12).

miR-574-3p inhibits TCF7L2 (Transcription Factor 7 Like 2), a protein acting as a transcription factor, and increases Wnt signaling pathway leading to increased malignant cells and cancer in these cases (11). On the other hand, miR-33-a plays a role in the growth and survival of tumoral cells by inhibiting this signaling pathway (13). In fact, TCF7L2 regulates the expression of genes involved in insulin signaling, metabolism, and cell proliferation. Mutations in this gene have been linked to an increased risk of type 2 diabetes and are also associated with an increased risk of certain types of cancer (10, 11). Studies interpret the intron 3 SNP rs7903146 as the causal variant within the TCF7L2 gene (13).

miR-133-a and miR-133-B inhibit IGFBP3 (Insulin-like growth factor-binding protein 3) gene are involved in the development of a variety of tumors in pediatric such as Wilms' tumor, osteosarcoma, and so on (12). In fact, inhibition of this gene by increasing the activity of PIK3/AKT/mTOR signaling pathway and also Wnt/beta-catenin leads to the induction of cell growth and proliferation. Therefore, epigenetic changes in this gene are associated with an increased risk of cancer in pediatric cases (14).

CDKN2A (Cyclin-Dependent Kinase Inhibitor 2A) encodes P16 protein, a key regulator of cell proliferation and aging. Changes in the expression of this gene are associated with a variety of cancers (15, 16).

Several microRNAs change the expression of the CDKN2A gene. MiR-9, miR-221 inhibition and increased PI3K/AKT/mTOR, signaling pathway activity and Wnt/beta-catenin, play a role in the development of cancer in these pediatric cases (15). On the other hand, hypermethylation of the promoter regions of this gene leads to the shutdown of the gene and its inhibitory effect on tumor formation and this is seen in different types of cancers in the children of mothers with GDM (15).

As a result, epigenetic changes caused by GDM can lead to cancer in children. Failure to regulate DNA methylation and demethylation processes can lead to aberrant gene expression patterns and affect critical genes and molecular pathways involved in cell growth, proliferation and tumor formation (17).

More research is needed to better understand the genes and specific molecular mechanisms affected by epigenetic changes associated with maternal GDM and their role in the development of pediatric cancer (7).

1-2. Hyperglycemia in GDM and risk of cancer

Hyperglycemia is a condition in which the incidence of cancer is increased in pediatrics. These conditions can be hereditary or due to maternal diabetes during pregnancy. Hyperglycemia leads to physiological changes and metabolic pathways that ultimately cause cancer in children (18). Hyperglycemia leads to the activation of NF-kB pathway and the production of inflammatory mediators such as TNF-α, IL-1 and TNF-β (19). Six-Transmembrane Epithelial Antigen of the Prostate 4 (STEAP4) is an indispensable membrane protein and anti-inflammatory protein. Production of TNF-α leads to increased expression of STEAP 4 (20). In another study, it has been shown that induction of STEAP 4 inhibits the HIf-1α/MAPK pathway and ultimately reduces inflammation and prevents cell disruption (18). Connexins are structurally related transmembrane proteins that assemble to form expression gap junctions and are named according to their molecular weight. In monocyte to endothelium adhesion, Connexin 43Cx43 is involved. CX43 is one of the factors that are increased in DM patients. CX43 activates the PI3K/AKT/NF-kB pathway and leads to inflammation (21). In addition, CX43 has an inhibitory effect on HIF-1α and prevents its expression (22). TGF-β is another cytokine that increases its production under hyperglycemia (18). It has been shown that this cytokine activates the P38/ERK/RAGE pathway by activating SMAD3/7, which ultimately causes epithelial mesenchymal transition (EMT) (23). Aldolase Reductase (AR) has also been found to increase fibrosis and EMT by TNF-α/miR-200a-3p/141-3p (24).

The production of inflammatory mediators has a dual role. On one hand, they lead to hyperglycemia and on the other hand, they cause the progression of cancer. Therefore, the identification of signaling pathways can play an important role in designing therapeutic strategies.

TGF-β also induces IGF expression (25). IGF interaction with its receptor leads to activation of the MTOR/MAPK/Akt pathway and inhibits apoptosis of cancer cells (26). AR has also been shown to inhibit miR-200-a/AKT pathway and leads to decreased Nrf2 expression and increased ROS (24). It has also been found that miR-423-5p decreases glucose and prevents hyperglycemia by targeting FAM3A/ATP/AKT PATHWAY (27). Although TGF-α reduces inflammation and prevents cancer from progressing in pediatric cases, it can increase cancer progression through fibrosis and EMT (28). Therefore, its dual role acts like a double-edged sword, and identifying its associated pathways can be considered as a therapeutic target.

In general, it can be said that hyperglycemia plays a dual role in the occurrence of cancer in pediatrics. On one hand, it causes inflammation and progression of cancer, and on the other hand, it inhibits the proliferation of cancer. Therefore, identifying the pathways related to it can be helpful in designing treatment strategies.

1-3. Hyperinsulinemia in GDM and risk of cancer

Hyperinsulinemia is another condition that can contribute to the occurrence of cancer in pediatrics. The OSR1/SPAK/NCC/WNK pathway is activated through hyperinsulinemia and leads to insulin production (29). The insulin production leads to TNF-α production. In addition, it activates the P38/MAPK pathway, which leads to the production of MMPs. The insulin induces TET1 expression through PI3K/AKT. TET1 increases GPER expression (30-32).

GPER stabilizes HIF-1α, which can play a role in EMT and lead to cancer. On the other hand, GPER inhibits the production

of MMPs and inhibits the IKK-β/NF-kB pathway, which leads to inhibition of cancer progression (33, 34).

IL-17 is one of the cytokines whose production increases through GPER. Additionally, insulin also leads to the production of this cytokine (35, 36). IL-17 triggers inflammation by activating the IL-6/STAT3/NF-kB pathway. It also increases the production of MMPs through the P38/MAPK/ERK/CEBP-β/NF-kB/AP-1 pathway (37, 38). It can be said that the production of IL-17 by insulin can play a role in the occurrence and progression of cancer. Therefore, targeting it can be a therapeutic path to treat patients.

Insulin also activates the PTEN/AKT/eNOS pathway, resulting in the production of NO. Furthermore, it inhibits miR-21 and reduces the production of endothelin-1 (ET-1). In previous studies, it has been shown that the production of NO leads to the inhibition of the P38/MAPK/ERK pathway and also the JAK/STAT3 pathway, which ultimately can suppress T cells and promote the proliferation of cancer cells (39, 40). On the other hand, the expression of miR-21 activates the ERK/AKT pathway and leads to the inhibition of PTEN expression. Ultimately, this results in the suppression of apoptosis in cancer cells (41).

In general, it can be said that insulin production can have a dual role in patients. On one hand, it can lead to molecular pathway alterations and cancer development, and on the other hand, it can result in inhibition of progression. Therefore, identifying the pathways associated with them can be helpful in patient management.

2- CONCLUSION

GDM is a condition that is spreading day by day. According to studies, the incidence of cancer in pediatrics has been shown to be related to GDM. Epigenetic changes, hyperglycemia and hyperinsulinemia are among the things that can contribute to the occurrence of cancer due to GDM. Identifying the upstream and downstream pathways of genes can play an important role in preventing the occurrence and progression of cancer. In addition, some genes have a dual role in the pathogenesis of cancer. Therefore, their identification can be helpful in designing treatment strategies.

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