나 혜 경 교수 지도

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Role of Obesity in Tumor Microenvironment

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성신여자대학교 일반대학원

식품영양학과

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ABSTRACT

Role of Obesity in Tumor Microenvironment

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Obesity is a serious social problem in the world and has been known to contribute the high risk of several chronic diseases including cancer. Epidemiologic studies have demonstrated that increased circulating levels of insulin, insulin-like growth factor (IGF)-1, leptin, inflammatory factors, vascular endothelial growth factor (VEGF) and plasminogen activator inhibitor (PAI)-1, are typically observed in obese individuals. Therefore, obesity is considered as an chronic inflammatory response, which is characterized by production of abnormal cytokine which trigger the proinflammatory signaling and modulate cellular differentiation, apoptosis, proliferation, and angiogenesis. Adipose tissue is an active endocrine organ and

secrets variety of hormones, bioactive peptides, and cytokines, termed adipokines, such as leptin, TNF-α, IL-6 and insulin & insulin like growth factor. Elevated levels of proinflammatory cytokines have been noted in the serum of asymptomatic obese individuals corresponding to the degree of obesity, including leptin, TNF-a, IL-6 and insulin & insulin like growth factor. These cytokines are regulated by the transcription factor NF-κB**.** NF-κB controls the expression of the genes linked with proliferation, invasion, angiogenesis, and metastasis of cancer. Tumor microenvironment is the cellular environment in which the tumor exists, including surrounding blood vessels, immune cells, fibroblasts, other cells, signaling molecules, and the extracellular matrix (ECM). The tumor microenvironment contributes to every aspect of carcinogenesis including malignant transformation, tumor growth, metastasis, and drug resistance. In chronic inflammation, proinflammatory cytokines such as TNF-α can induce DNA damage through generation of reactive oxygen/nitrogen species (ROS/RNS), which leads to tumor initiation. Growth factors, ROS, RNS, and cytokines released from inflammatory cells lead to genomic alterations in the epithelium and subsequent cancer initiation. Thease cytokines can promote malignant transformation through epithelial-mesenchymal transition (EMT). Tumor growth and invasion are also favored by proinflammatory cytokines that stimulate cell proliferation, reduce apoptosis, and enhance EMT and angiogenesis. Dietary fat also associated with tumor microenvironment. Dietary fat increases solid tumor growth and could prolong mortality. Several studies reported that HFD diet (60% kcal fat) induces tumor growth and progression through EMT and inflammatory response in a mouse xenograft tumor model. Dietary fatty acid, such as arachidonic

acid and oleic acid present esterified form in cell membrane phospholipids promote MAPK activation and mediate the adhesion, migration and invasion. Chronic hypernutrition such as high level of dietary saturated fatty acids (SFA) and trans-fatty acids stimulates intracellular pathways leading to oxidative stress through multiple biochemical mechanisms include hypoxia, therefore, a low grade oxidative condition is unbroken. Hypoxia promotes growth stimulatory functions or enhanced pro-tumorigenic and angiogenesis and metastasis. In conclusion, this review is mainly focused on effects of several cytokines derived from accumulated adipocytes on carcinogenesis, particularly obesity-associated tumor microenvironment and their underlying molecular mechanisms.

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Ⅰ. Introduction

World Health Organization(WHO) defines overweight and obesity as "abnormal or excessive fat accumulation that may impair health." The fundamental cause of overweight or obesity is a positive energy balance, in which energy intake exceeds energy expenditure over a prolonged time leading to the increased body mass [1](Fig 1). Obesity heightens the risk of several chronic illnesses including cancer development [2,3,4]. Epidemiological data suggest a significant association between increased body mass index or obesity and several cancers such as pancreatic cancer [5], prostate cancer [6], breast cancer [7], etc(Table 1). In 2007, the World Cancer Research Fund (WCRF) reported that body fatnesses is associated with an increased risk of various cancers [8].

The cancer cells recruit vascular and lymphatic endothelial cells, pericytes, fibroblasts, macrophages and other hematopoietic cells by generating the chemoattractant signals. These cells together with extracellular matrix (ECM) and basement membrane constitute the microenvironment of tumor cells [9], termed tumor microenvironment. The tumor can influence the microenvironment by releasing cytokines into the surrounding tissue or into the bloodstream [10]. The interaction between these cytokines and the tumor microenvironment affects tumor growth and remodeling of the tumor microenvironment. Adipocyte hypertrophy and excessive adipose tissue accumulation participates as a central mediator of this inflammatory response in obese individuals by lead to secreation of insulin-like growth factor-1 (IGF-1) and proinflammatory cytokines [11] such as tumour necrosis factor (TNFα),and interleukin (IL)-6. These cytokines

produced from adipocyte increased survival and growth of cancer cells [12]. Increased blood levels of insulin, insulin-like growth factor-1 (IGF-1), oestrogen, interleukin (IL)-1, IL-6, IL-17, tumour necrosis factor (TNFα), leptin and other inflammatory markers were observed in the cancer patients with obesity[5,6,7,8,9]. Obesity may globally contribute to onset of carcinogenesis through nutrient sensitive signaling cascades [13], such as the insulin/insulin-like growth factor (IGF-1) [14] and PI3K/ Akt/ mammalian target of rapamycin (mTOR) pathways [15], which driving cell proliferation, cell growth and anti-apoptosis pathways (Figure 2).

Obesity-associated carcinogenesis has been known to be driven by chronic inflammation induced by cytokines from adipocytes. Low level of adiponectin and high level of leptin and soluble tumor necrosis factor receptor 2 (sTNF-R2), and other cytokines are positively associated with the progression from inflammation to metaplasia and neoplasia [16]. Subjects who developed cancers had significantly higher level of hsCRP, IL-6, sTNFR2 and lipocalin 2. The risk of malignancy increases by chronic low grade inflammation related to central obesity [17]. The most of studies on molecular mechanisms underlying obesity-asscociated carcinogenesis focus on inflammation pathways. However, recent study suggest that cytokines produced from adipocytes cells can effects the tumor microenvironment and trigger the cancer progression and promotion [18]. Therefore, this review highlights correlation of obesity-induced chronic inflammation and tumor microenvironment and deal with its underlying molecular mechanisms.

Table 1. The relative risk between obesity and cancer.

Cancer type	RR/OR (95%CL)	Factor	Reference
Pancreatic cancer	2.8	BMI > 40 kg/m^2, female	[5]
Prostate cancer	1.5	Cancer mortality	[6]
Breast cancer	2.3	Cancer stage (III , IV)	[7]
Renal cancer	1.6	BMI ≥ 30 kg/m^2	[19]
Colon cancer	1.1	Weight per 5kg/m^2, Men	[20]
Gastric cancer	3.9	BMI≥28 kg/m^2	[21]
Liver cancer	1.7	BMI > 25 kg/m^2	[22]
Lung cancer	0.8	BMI ≥ 25 kg/m^2	[23]
Badder cancer	1.3	BMI> 24.9 kg/m^2	[24]
Melanoma	1.3	BMI > 25 kg/m^{2,} Male	[25]
Leukemia	2.9	High BMI z-score	[26]

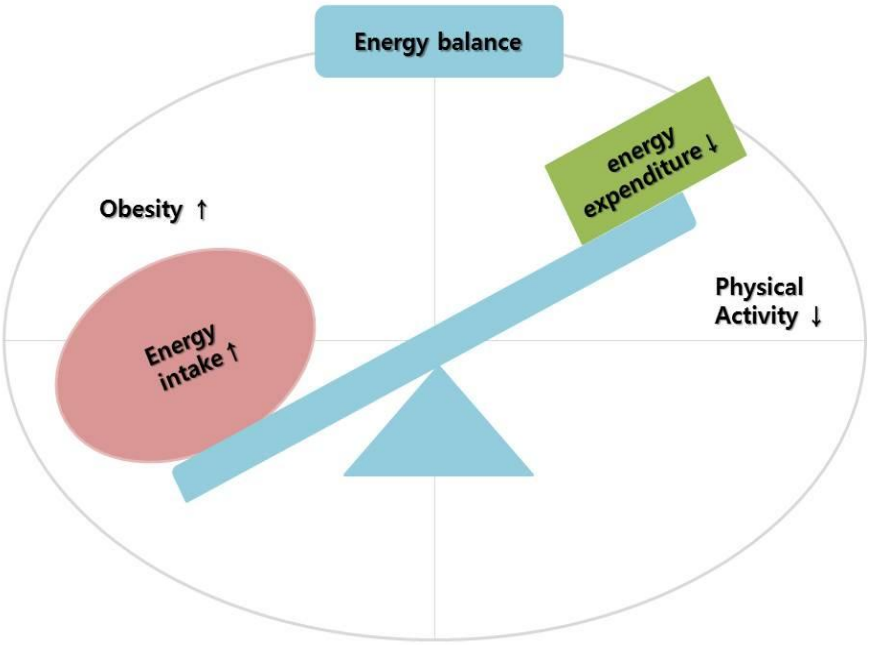

Figure 1. Energy homeostasis and obesity The fundamental cause of overweight or obesity is a positive energy balance, in which energy intake exceeds energy expenditure over a prolonged time leading to the increased body mass.

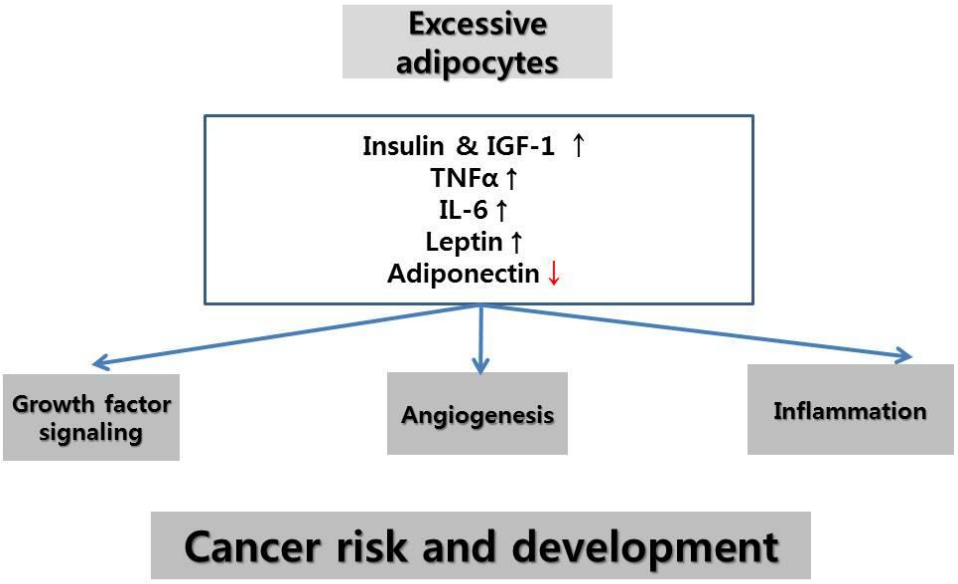

Figure 2. The molecular mechanisms by which obesity-induced carcinogenesis. Obesity may globally contribute to onset of carcinogenesis through nutrient sensitive signaling cascades, such as the insulin/insulin-like growth factor (IGF-1) and PI3K/ Akt/ mammalian target of rapamycin (mTOR) pathways.

Ⅱ. Molecular mechanisms underlying carcinogenesis of hormones or cytokines derived from adipocytes

Isulin, insulin like growth factors, and adipokines (e.g adiponectin and leptin), and obesity-related inflammatory cytokine derived from adipocytes have been known to be involved in carcinogenesis (Figure 3).

1. Insulin & insulin like growth factors

Metabolic consequences of obesity include increased circulating levels of insulin and bioavailable IGF-1, and altered levels of adipokines, such as leptin and adiponectin, cytokines, such as IL-6, TNFα, etc [27]. Insulin increases the bioactivity of IGF-I by enhancing IGF-I synthesis and by reducing hepatic protein production of the insulin-like growth factor binding proteins 1 (IGFBP-1) and 2 (IGFBP-2) [28]. Chronic hyperinsulinemia caues abnormal cellular proliferation and inhibition of apoptosis by induced PI3K/Akt/mTOR signaling [29]. Tumor growth is angiogenesis-dependent [30], and suppression of angiogenesis has been shown to inhibit tumor growth [31].

2. Adiponectin

Adiponectin is the most abundant adipokine secreted by fat cells [32] and acts as an antiatherogenic hormone through the inhibition of proliferation of vascular smooth muscle cells and endothelial cells [33,34]. Adiponectin is decreased in obesity and

deficient in lipoatrophy, and that reduction plays causal roles in the development of insulin resistance [35]. In addition, adiponectin activates peroxisome proliferator-activated receptor (PPAR-α) [36], a transcription factor and a major regulator of lipid metabolism in the liver [37], thereby enhancing fatty acid combustion and energy consumption leading to a tissue decrease content of triglycerides in the liver and skeletal muscle, and improving insulin sensitivity *in vivo* [36]. It was reported that the level of adiponectin decreased in the cancer patients [38], cell lines [39], animal models [40]. The molecular mechanisms of tumour inhibition with adiponectin involves inactivation of mitogen-activated protein kinase(MAPK) 1/3, and ERK1/2 and concomitant reduced glucose uptake [41].

3. Leptin

Leptin is a 167 amino acid product of the *ob* gene, it has indirect effects on hypothalamic pathways and modulates immune function, cytokine production, angiogenesis, carcinogenesis, and other biological processes [42]. Obesity can lead to alterations in leptin regulation. Chronic overexpression of leptin induces leptin resistance, resulting in increased circulating leptin [43,44]. Leptin binds to the transmembrane receptor (LRb) that contains intracellular tyrosine residues that become phosphorylated activates STAT3 and its down stream signal molecules including ERK [45]. This is followed by induction of Janus-kinase (JAK) phosphorylation and subsequently STAT3 phosphorylation [46]. STAT3 activated by tyrosine phosphorylation at position 705 leading to its dimerization, nuclear translocation, DNA binding, and activation of gene transcription involved in anti-apoptotic, pro-

proliferative and immune response genes [47].

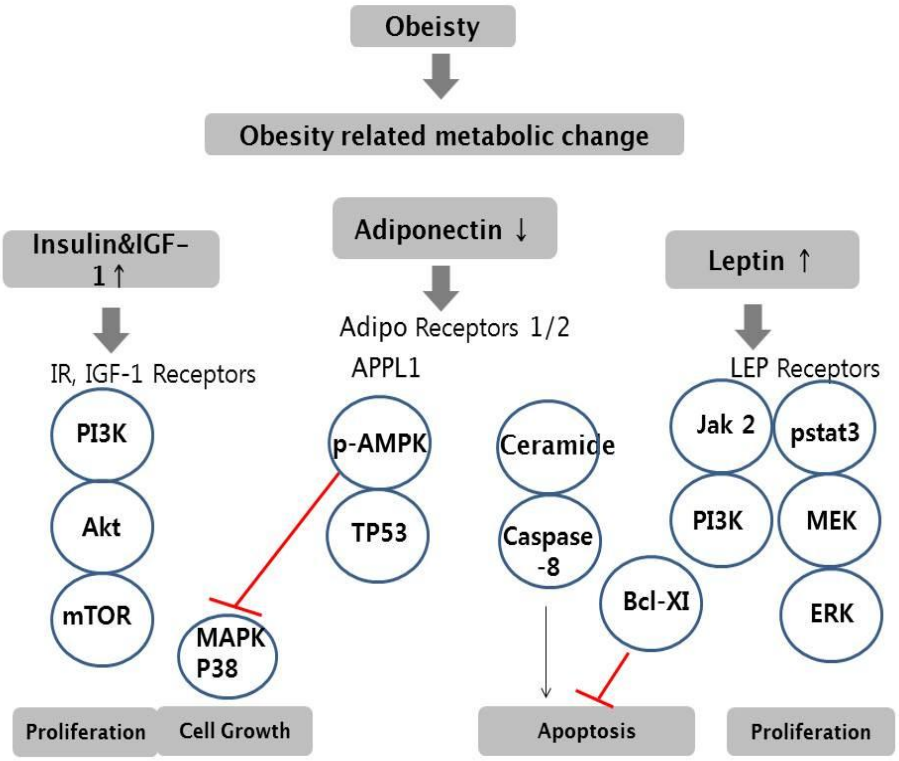

Figure 3. The molecular mechanisms of obesity-associated carcinogenesis. Obesity-induced adipocytes secrete insulin, insulin like growth factors and adiponectin, and leptin. These hormones or cytokines activates cellular signal molecules involved in cell growth and proliferation and inhibites apoptotic pathways.

Ⅲ. Obesity-induced inflammatory cytokines are implicated in tumor microenvironment

Obesity-induced inflammation results in the infiltration of macrophages and the release of proinflammatory cytokines, which could exacerbate end-organ damage and cell apoptosis via the caspase-dependent signaling pathway [48].

1. Adipokines is involved in epithelial-mesenchymal transition

The tumor microenvironment is the cellular environment in which the tumor exists. In detail, soluble factors released from tumor cells, such as chemokines, cytokines, and growth factors, i) recruit inflammatory cells, fibroblasts, and myeloid cells; ii) reshape the extracellular matrix and iii) initiate and support neovascularization [10]. Components of the tumor microenvironment are uncontrolled cellular proliferation and newly synthesized blood and lymph vessels that are driven by the metabolic needs of proliferating cells, including oxygen and nutrients, and are mediated by pro-inflammatory cytokines [49]. Epithelial cells(ECs), the predominant cells of origin of adult cancer, exist in contiguous sheets composed of organized, polarized cells circumscribed by a basement membrane that separates the epithelium from the stroma [50]. ECs control vascular repair, and vascular health is defined by endothelial integrity [51].

To acquire malignancy, cancer cells must undergo a loss of epithelial phenotypes and acquire characteristics of a mesenchymal state [52]. Epithelial-

mesenchymal transition (EMT) is a morphogenesis process involved in embryonic and organ development [53]. The features of EMT include loss of cell adhesion molecules, downregulation of the expression of epithelial differentiation markers and increased expression of mesenchymal markers [54,55]. It was reported that adipokines contributes to development of EMT [50].

1)TNFα

TNFα is a major player in regulation of cell growth, differentiation, inflammation, and metastasis [56]. Elevated levels of TNFα along with its receptors have been strongly associated with a high risk of endometrial cancer [57]. In breast cancer patients, transcription levels of TNFα were significantly higher by 1.4-fold and 2.1-fold in blood cells of overweight/obese individuals respectively than those observed in lean control subjects [58]. TNFα produced by tumor cells is known to enhances EMT through down-regulation of E-cadherin expression and up-regulation of MMP-9 and CD44 expression, a marker of cancer stem cell, in carcinomas of renal cells [59]. In addition, TNFα induced invasive morphological changes such as lower cell stiffness and increased cell motility in human gastric cancer cell [60]. Moreover, TNFα-induced EMT is related closely to the primary tumor stage, distant metastasis, and poor prognosis and also invasion in cancer cell lines. Molecular mechanisms underlying TNFα-induced EMT in various experimental models are shown in Table 2. In addition, high-fat diet-induced obesity increased the expression of TNFα in the colon by 72% (P=.004) and that of interleukin-18 by 41%(P=.023) in C57BL/6 mice. TNFα

protein induced phosphorylation of glycogen synthase kinase 3 beta (GSK3β), an important intermediate inhibitor of *Wnt* signaling in the colonic mucosa of obese mice(P<.02) [61]. TNFα also has been known to regulate NFκB, Akt, and p38 MAPK [62,63,64].

Table 2. TNFα contribute to epithelial-mesenchymal transition in various cancer cells.

Type	Effect	Mecahnism	Refer ence
Renal cancer	Increase of tumor stage and metastasis	↓E-cadherin ↑MMP-9, CD44	[59]
Renal cancer	Induces EMT, promote tumor growth and metastasis	↑GSK3β-dependent	[65]
Renal cancer	enhance invasion and EMT	↓E-cadherin ↑Vimentin expression ↑MMP-9 activity	[66]
Gastric cancer	Induce invasion	↑MEK - ERK signal	[60]
Colon cancer	Proliferation in the colonic cancer cells	↑ TNFα protein level by Phosphoryl ation of GSK3β(inac tivity) and elevated expression of c-myc	[61]
Pancreatic cancer	Promote migration and invasion in	↑ Snail-1 protein levels in the presence of TNF	[67]

2) IL- 6

IL-6 is a glycoprotein consisting of 212 amino acids encoded by the IL-6 gene localized on human chromosome 7p21–14 [68]. IL-6 binds to the IL-6 receptor (IL-6R), which exists in a membrane-bound (mIL-6R) and soluble form (sIL- 6R). IL-6 is a multifunctional cytokine that plays a key role in both innate and acquired immune responses, hematopoiesis, inflammation, and the regulation of growth and differentiation of cancer cells [69]. Also, IL-6 is a pleiotropic cytokine produced by various cells including macrophages, B cells, T cells, syncytiotrophoblasts, and etc [70]. In fanconi anemia cells, IL-6 is overexpressed due to EMT by NF-κB/TNFα dependent mechanism, leading to promoting the proliferation, migration, and invasion of surrounding tumor cells [71].

IL-6 signaling activates the Janus kinases JAK1, JAK2 and TYK2 which lead to the phosphorylation of signal transducers and activators of transcription-1 and -3 (STAT1 and STAT3). IL-6 activates the Ras-MAPK and PI3K-Akt signaling pathways which also contribute to its anti-apoptotic and tumorigenic function [72,73]. Obesity-promoted hepatocellular carcinoma(HCC) development was dependent on enhanced production of IL-6. In addition, the absence of IL-6 prevented the obesity-induced increase in JNK and ERK phosphorylation in non-tumor liver and HCCs and completely reversed the decrease in p38 phosphorylation previously seen in HCCs of obese mice [74]. IL-6 funtion in EMT was summarized in the Table 3.

Table 3. IL-6 contributes to in epithelial-mesenchymal transition.

Type	Effect	Mecahnism	Refere nce
Bladder cancer	Promote tumor growth and invasion	↑STAT3 signaling	[75]
Breast cancer	Ativate breast stromal fibroblasts	↑Expression of RNA-binding Protein AUF1	[76]
Breast cancer	Promotes the generation of breast cancer stem-like cells analogous	↑Induced EMT	[77]
Cervical cnacer	Promoted cell growth and altered cell morphology	Induced EMT by STAT3	[78]
Colon cancer	Promote colon cancer invasion and metastasis	↓miR-34a, ↑STAT3	[79]
Colon cancer	Acquisition of cellular phenotypic changes : increased invasion and decreased response to cytotoxic stresses	↓p53 ↑c-MYC mRNA ↓E-cadherin level	[80]
Lung cancer	Enhanced the tumor forma tion	↑TGF-β signaling	[81]
Melanoma	Enhanced invasion	↑Twist ↑N-cadherin ↑p-STAT3	[82]

3) Leptin

Chronic overexpression of leptin induces leptin resistance, resulting in increased circulating leptin [43,44]. High level of leptin was observed in cancer patients and have several protumorigenic activities [45]. Leptin modulates the expression of various gene products that are regulated by β-catenin and potentiates tumor cell migration and invasion. It is speculated that leptin might mediate its effects on EMT through modulation of the Wnt/β-catenin pathway [83]. Leptin increases accumulation and nuclear translocation of β-catenin leading to increased promoter recruitment. Mechanistically, leptin stimulates phosphorylation of GSK3β via Akt activation resulting decrease in the formation of the GSK3β-LKB1-Axin complex that leads to increased accumulation of β-catenin [83]. In addition to leptin promotes metastasis through upregulate TGF-β at both mRNA and protein levels and EMT in A549 lung cancer cells [84].

4) IGF-1

IGF-1 is a peptide growth factor that shares 50% sequence homology with insulin. Obesity leads to insulin resistance, hyperinsulinemia and greater bioavailability of IGF-1 [85]. Hyperinsulinemia stimulates pro-inflammatory as well as lipogenic processes, exacerbating obesity and inflammation [86,87]. IGF stimulated phosphorylation of IGF-IR and simultaneously activates Src. Because the tyrosine kinases of IGF-IR and Src participate in activation of Akt [88]. IGF-1 signaling has been shown to have strong implication in the EMT process. IGF-1 levels and activity have been closely examined in proliferative tissues for their

relationship to changes in cellular morphology associated with cancer progression [89]. Relationsip between IGF-1 and EMT is as follow in Table 4.

IGF-1 upregulates expression of Mucin 1 (MUC1), a transmembrane glycoprotein, expression via activation of PI3K/Akt or MAPK pathway in breast cancer cells [90]. The overexpression of MUC1 is critical for IGF-1-induced EMT of MCF-7 cells. The knockdown of MUC1 prevented by various EMT markers including the downregulation of expression of E-cadherin, up-regulation of N-cadherin, vimentin, and fibronectin in MCF-7 cells. Silencing of MUC1 decreased nuclear location of β-catenin with or without IGF-1 (200 ng/ml) [91]. Also, IGF family molecules bind to a variety of insulin-like growth factor receptors (IGFRs). These receptors are receptor tyrosine kinases (RTKs) and most frequently activated through PI3K and MAPK dependent mechanisms [92]. Elevated IGF-1 increases invasive and active Matrix metalloproteinases (MMPs), zinc-dependent endopeptidases, and activation of latent TGF-β1 induced EMT in breast cancer cells through signals transduced via the PI3K and MAPK pathways [93].

Table 4. IGF-1 contribute to epithelial-mesenchymal transition.

Type	Effect	Mecahnism	Refer ence
Breast cancer	Overexpression of MUC1 contributes to metastases	↑PI3K/Akt signaling	[91]
Breast cancer	Activates MMPs and induces invasion	Increased IGF-1 expression induced the -catenin/TCF pathway Activation of PI3K and MAPK pathways	[93]
Esophag eal cancer	Promotes cell invasion and motility	Phosphorylation of SMAD 2/3 and promote switch from E-cadherin-to-N-cadherin Induction of TGF-	[94]

2. Obesity-induced inflammatory cytokines have cancer cell adhesiveness

Cancer dissemination is initiated by decreased cell-cell adhesion and increased motility and invasive properties [95]. Circulating tumor cells(CTC) can interact and adhere to the endothelial lining of the vasculature through a series of receptor-mediated events, commonly referred to as the metastatic adhesion cascade [96]. Firm adhesion of CTCs on the endothelium then allow extravasation and subsequent secondary tumor site formation [97]. It was reported that cytokines or hormones released from adipocytes are involved in tumor associated adhesion (Table 5).

IL-6 was increased expression in hepatocytes depending on cancerous malignancy and expression TM4SF5 [98], is known as the tetraspanin family a cell-surface proteins [99]. IL-6 treatment activated Focal adhesion kinase(FAK), a non-receptor cytoplasmic tyrosine kinase [100], STAT3 and enhanced focal adhesion (FA) formation in TM4SF5-null cells [101]. Also, leptin receptor Ob-Rb receptors are connected with several signaling pathways involved in cell proliferation, apoptosis and cancer progression [102]. Leptin enhanced cell invasion and adhesion through activated JAK and ERK signaling in the CRC cell lines [103].

Table 5. The cytokines released from adiopocyte have cancer cell adhesiveness.

Obesity factor	Effect	Mecahnism	Refer ence
IL-6	Enhanced focal adhesion (FA) formation and imm une escape of human liver cancer cells.	Activated FAK and STAT3 by the IL-6-STAT3 pathway	[101]
Leptin	Induced adhesion and invasion and increased the number and size of sphere oid formation in CRC cell lines	Activated JAK and ERK signaling	[103]
TNF-α	Enhanced fusions between oral squamous cell carcinoma cells and endothelial cells	VCAM-1and VLA-4 pathwa y	[104]
Cox-2	Increase in the migration of MDA-MB-231 cells.	Increase in the p-Src and p-FAK	[105]

3. Obesity-associated factors are implicated in hypoxia

Hypoxia is a characteristic of the tumor microenvironment that may play a critical role in tumor angiogenesis, survival response, invasion and metastasis [106]. To survive in this hypoxic microenvironment, tumor cells co-opt adaptive mechanisms to switch to a glycolytic metabolism, promote proliferation, become resistant to apoptosis [106]. Some of obesity-associated factors have been implicated in hypoxia (Table 6).

During times of positive energy balance, adipose tissue absorbs the energy surplus by increasing both cell size and number [107]. The increased adipocyte size requires oxygen to diffuse over longer distances prior to reaching adipocyte mitochondria. The partial oxygen pressure (20 mmHg versus 40 mmHg) in obese versus lean mice were decreased [108,109,110]. Therefore, obesity a low grade oxidative condition [111] called hypoxia. Hypoxia activates IGFBP3 transcription through HIF-1α [112]. IGFBP3 is a hypoxia-inducible gene and contributes to tumor progression with a concurrent induction of a subset of tumor cells showing high expression of CD44 (CD44H) implicated in invasion, metastasis and drug resistance in xenograft transplantation models with esophageal cancer [113]. IGFBP3 also cooperates with hypoxia to mediate the enhancement of population CD44Hcell by suppressing reactive oxygen species (ROS) in an IGF-independent fashion [113]. High level of IL-6 was secreated under hypoxic conditions [114].

Leptin gene is transcriptionally activated in response to hypoxia through a mechanism that involves binding of the heterodimer HIF1α/β to a functional

hypoxia-responsive elements(HRE) site located within the proximal promoter region [115]. Ob-R expression co-localized with HIF-1α in consecutive sections of pancreatic cancer tissues. In addition, Ob-R levels significantly correlated with HIF-1α levels in pancreatic cancer patients(rs = 0.434, p < 0.001). over-expression of HIF-1α up-regulated the transcription of Ob-R promoter in Human pancreatic cancer cells MIA PaCa-2 (~4.8 fold) and CFPAC-1 cells (~4.4 fold) [116]. TNFα activates expression of the inhibitory PAS domain protein (IPAS) to suppress the hypoxic response caused by HIF-1/2 in rat pheochromocytoma PC12 cells. This induction of IPAS was dependent on NF-κB pathway and attenuated hypoxic induction of HIF-1 target genes such as tyrosine hydroxylase (TH) and VEGF [117].

Table 6. The cytokines released from adiopocyte are involved in hypoxia-induced carcinogenesis.

Obesity Factor	Effect	Mecahnism	Refer ence
IGFBP3	Promote tumor growth in esophageal cancer	hypoxic induction of CD44H cells via an IGF-independent mechanism.	[113]
IL-6	Enhance migratory potential and cell survival in breast cancer cells	Activate Stat3 and down stream effectors to enhance themigratory potential of hMSCs under hypoxia	[118]
Leptin	Promote transcriptional regulation of VEGF gene in breast cancer cells	the activation of several TF (HIF-1α, AP1, NFκB and SP1) via PI-3K/AKT1 and MAPK/ERK 1/2 signalling	[119]
Leptin	Enhanced migration, agiogenesis and Survival of MSCs	Increased leptin and cell surface receptor CXCR4	[120]
TNF-α	Suppresses the hypoxic response in PC12 cells	Induction of inhibitory PAS domain protein in NFκB-dependent	[117]
Insulin	Enhance the prolifera tion and invasion of PANC-1 cells	Increased expression of HIF-1α	[121]

4. Free fatty acids are involved in tumor microenvironment.

HFD-induced obesity has been shown to increase development of AOM-induced aberrant crypt foci in the colon [122]. High-fat diets are known to induce obesity in humans and rodents [123,124]. A diet containing 23% corn oil (rich in the omega-6 fatty acid linoleic acid) increased the tumor growth rate and lung-metastasis incidence of MDA-MB-435 human breast cancer cells injected into the mammary fat pads of athymic nude mice [125]. Long-term consumption of a 60% kcal-fat diet increases solid tumor growth and metastasis of 4T1 murine mammary carcinoma cells and mortality in obesity-resistant BALB/c mice [126]. In addition, dietaty fat induce EMT and inflammation by activate oncogenic pathways such as PI3K/Akt/mTOR and MAPK/ERK signaling in cancer [127]. Consumption of high-fat diet induces EMT and inflammation in a mouse xenograft tumor model via suppression of p21CIP1/WAF1 expression and increases in enhancement of nuclear histone deacetylase complex (HDAC). In addition to HFD could mediate the disassembly of E-cadherin adherent complex and the up-regulation of vimentin and N- cadherin proteins in tumor tissues [128]. HFD consumption could play important roles in tumor growth and progression including EMT and tumor inflammation in a mouse xenograft model.

Arachidonic acid (AA), n-6 polyunsaturated fatty acid, present in an esterified form in cell membrane phospholipids [129]. AA promotes MAPK activation and mediates the adhesion of MDA-MB-435 breast cancer cells to type IV collagen. AA promotes phoshorylation of Src and FAK in MDA-MB-231 cells [105]. AA enhances the migration and invasion of MDA-MB-231 breast cancer cells through

activation of PI3K-AKT-NFκB signaling pathway [130]. Linoleic acid (LA) is an essential and the major poly-unsaturated fatty acid (PUFA) in most diets, and is required for the biosynthesis of eicosanoids. LA induces inappropriate inflammatory responses [131,132]. On the EMT process, LA induces proliferation and invasion through down-regulation of E-cadherin expression, accompanied with an increase of Snail1/2, Twist1/2 and Sip1 expressions in breast cancer cells. LA induces FAK and NFkB activation, MMP-2 and -9 secretions. LA promotes an EMT-like process in MCF10A human mammary epithelial cells [133].

Epidemiological, clinical, and animal studies have shown that obesity is coupled with altered redox state and increased metabolic risk. Chronic hypernutrition, high fat high carbohydrate meals, as well as high dietary saturated fatty acids and trans-fatty acids, stimulate intracellular pathways, leading to oxidative stress through multiple biochemical mechanisms, such as superoxide generation from NADPH oxidases (Nox), oxidative phosphorylation, glyceraldehyde autoxidation, protein kinase C activation, and polyol and hexosamine pathways [134].

Given these findings suggested that dietary fat can be contribute to carcinogenesis by influencing the tumor microenvironment. Proinflammatory cytokines such as TNFα, IL-6, and leptin, etc secreted from obesity-induced adipocytes induced EMT and decreased cell-cell adhesion and increase invasion for tumor growth and metastasis. High-fat diet promotes production of theses cytokines by excessive accumulation of adipocytes. Whereas, dietary restriction (DR) reduces tumor load by lowering the adhesion of circulating tumor cells to

hepatic vascular endothelium. DR reduces mRNA expression of E-selectin, an endothelial cell specific adhesion molecule[28], and hepatic tumor load. DR also downregulates the production of proinflammatory cytokines and adhesion molecules in models of renal and hepatic ischemia–reperfusion injury [135]. CR suppressed M- Wnt and E- Wnt tumor progression and inhibited EMT and intratumoral adipocyte accumulation [136]. In addition, calorie restricted diet was significantly curtailed cancer growth and metastasis than high energy diet by downregulation of Akt-mTOR activity and upregulation of AMPK and SIRT1 in ovarian cancer cells [137].

In contrast, docosahexaenoic acid (DHA) blocks the invasiveness of PC3 prostate adenocarcinoma cells because TGF-β-stimulated prostate fibroblasts and prevents EMT by DHA inhibited secretion of MMT and capacity of TGF-b-stimulated NCAF (non-cancer-associated fibroblasts) induced EMT such as c-Met and E-cadherin [138]. Omega6 fatty acids is increase the cell adhesion and induces EMT and promote the cacinogenesis. Omega 6 fatty acids and in order to more accurately the relationship between the tumor microenvironment is to construct a food model arachidonic acid is rich, This not only cancer cells, even in normal cells omega6 fatty acids There will be necessary of additional experiments to generate cancerous through the changes in the tumor microenvironment.

Ⅳ. Conclusion

Obesity has been known to contribute the high risk of various cancers. Obesity-associated carcinogenesis is associated with inflammation induced by cytokines and hormones released from adipocytes. Inflammatory cytokines, leptin, adiponectin, and IGF have been to associated with tumor microenvironment including EMT, cell ahdsion and hypoxia. Dietary fatty acid, such as arachidonic acid and oleic acid present esterified form in cell membrane phospholipids promote MAPK activation and mediate the adhesion, migration and invasion. Chronic hypernutrition such as high level of dietary saturated fatty acids (SFA) and trans-fatty acids stimulates intracellular pathways leading to oxidative stress through multiple biochemical mechanisms include hypoxia, therefore, a low grade oxidative condition is unbroken. Hypoxia promotes growth stimulatory functions or enhanced pro-tumorigenic and angiogenesis and metastasis. However, the molecular mechanisms underlying obesity-associated tumor microenvironment remain largely unknown.

CR and/or omega 3 fatty acids have been shown to exert anti-carcinogenic effects through inhibition of signal molecules involved in inflammation and tumor microenvironment. The main causes of obesity are associated with high consumption of calory and fat and low expenditure of energy. Moreover, moderate exercise has been known to inhibit or retard the carcinogenesis. Therefore, CR and expenditure of energy through exercise can be expected as a reliable strategy for cancer prevention.

논문개요

비만은 암의 발생을 비롯한 여러가지 만성 질환의 위험성을 높이는 주요한 원인으로 인식되고 있다. 비만과 암의 관련성은 비대한 지방세포에서 분비된 염증인자들에 의한 만성 염증상태 및 비만세포의 축적으로 기인한 저산소증과 같은 유사한 미세환경에 기인한다. 비만으로 인한 염증상태는 인슐린저항성을 야기하여 인슐린이 인슐린 수용체에 결합으로써 세포 신호조절인산화효소 (extracellular-signal-regulated kinase) 그리고 phosphotidylinsositol-3 kinase (PI-3K) pathways 를 통해 세포 내 signalling cascades 를 활성화 한다. 이러한 신호체계는 유사분열을 촉진하는 세포사멸억제(anti-apoptotic)단백질의 발현을 통해 세포자살을 억제한다. 또한, 비만세포에서 분비하는 아디포카인(adipokine)들은 다양한 호르몬, 렙틴, 아디포넥틴과 같은 아디포카인들은 세포분화와 세포자살, 세포증식 및 초기혈관생성 (angiogenesis)을 조절한다. 비만은 만성염증반응으로 비정상적 사이토카인 생성을 증가시켜 pro-inflammatory signaling pathways 를 활성화한다. TNF-α, resistin, MCP-1, IL-6, IL-1 와 같은 proinflammatory cytokine 들은 비만정도와 상관관계를 나타낸다. 전사인자 NF-κB 는 인슐린의 유사분열촉진, 세포자살 억제 유전자, 암세포의 세포증식, 침윤, 혈관형성 그리고 전이와 관련된 유전자의 발현을 조절한다. 비만으로

인한 지속적인 염증상태는 암세포의 생존에 유리한 미세환경을 구축한다. 종양미세환경으로 암화과정을 촉진할 수 있는 Vascular endothelial growth factor IL-6 와 같은 용해성인자들이 해당된다. 세포와 세포, 세포외 구성물질, 기질세포 및 침윤하는 면역세포와 종양세포들이 이러한 용해성인자들을 활성/분비하거나 혹은 세포외기질을 손상시킴으로써 세포증식 및 분화과정이 활성화 된다. 이외에도 상피세포의 유전적 안정성과 DNA 보수(repair)능력 감소, 세포사멸 신호와 암화과정에 추가적으로 필요한 유전적인 변화, 상피-간엽세포 전이(epithelial mesenchymal transition)를 통해 종양세포로 변화를 초래한다. 그런데 지방세포에서 분비되는 pro-inflammatory cytokine 인 TNF-α, IL-6 그리고 렙틴 뿐만아니라. 인슐린유사인자(Insulin like growth factor-1) 증가가 종양미세환경의 암 발생 및 진행을 위한 성장신호와 세포자살억제, 혈관신생촉진에 관여하는 것으로 알려졌다. 또한, 비만관련 인자들은 혈중 순환하는 종양세포를 혈관 내 접착하여 다른 조직으로 침윤할 수 있도록 하는 세포의 접착능력을 증가시킴으로써 종양세포의 침윤과 전이 반응에도 관여한다. 비만은 고지방 섭취와 관련이 있는데, 고지방식이로 유도된 비만 동물/세포 모델 연구에 따르면, 식이지방 증가는 암세포의 성장을 촉진시키고, 생존을 연장시킨다. 또한 상피세포를 기질세포로 형질을 전환시키는 과정을 유도하며, 염증반응을 가속화한다. 아울러 오메가 6 지방산으로 알려진 아라키돈산이나 리놀레산 등으로부터 활성화되는

아이코사노이드(eicosanoids) 경로는 염증 촉진 및 암세포의 성장, 침윤, 혈관형성 촉진 등에 관여하는 것으로 잘 알려져 있다. 이외에도 최근 연구 결과에 따르면 오메가 6 지방산들이 세포의 암적 기능(세포부착, 형태의 변화, 세포의 형질전환, 세포이동 등)에 관련된 인자들과 상호작용 함으로써 발암 과정 뿐만 아니라 종양미세환경에도 영향을 미치는 것으로 알려졌다. 결론적으로, 이 논문에서는 고지방식이 섭취로 발생되는 비만세포의 축적으로 분비되는 사이토카인들이 종양이 형성되기 좋은 종양미세환경을 형성함으로써 암화과정에 관여함을 분자적 수준에서 제시해보았다. 아울러 식이지방 조성이 비만으로 인한 암발달 및 진행에 중요한 역할을 함을 제시하였다.

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