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Review Article

Adipocyte–Tumor Cell Metabolic Communication in the Advancement of Cancer

Faseeha Nadeem, Asima Tayyeb
School of Biological Sciences, University of the Punjab, Lahore, Pakistan

Abstract
The tumor-microenvironment (TME) can be defined as an ecosystem comprising various factors including predominantly immunosuppressive cytokines, Tumor-Associated Adipocytes (TAAs) and infiltrating immune cell population (dendritic cells, macrophages, B and T lymphocytes) surrounding a tumor. TME has emerged as a key player in cancer progression, mainly the molecular interaction between tumor cells and its neighboring adipocytes. Adipocyte-derived extracellular vesicles play a pivotal role in cancer invasion by enhancing fatty acid oxidation through the delivery of both fatty acid substrates and essential protein machinery. Interestingly, tumor cells actively induce lipolysis in TAAs promoting the lipolysis that serves as an energy source to fuel tumor growth. Furthermore, the heightened mitochondrial activity in tumor cells leads to the redistribution of mitochondria toward membrane protrusions facilitating cell migration in the presence of adipocyte-derived extracellular vesicles. Collectively, these complex interactions promote cancer cells invasion. Current review provides a comprehensive understanding of the contribution of adipocyte-derived extracellular vesicles in mediating physiological interaction between tumor cells and neighboring adipocytes with a specific emphasis on the tumor advancement.

Keywords: Adipocytes, Tumor-microenvironment, Tumor-associated adipocytes, Cancer

Adipocytes and Adipogenesis

White adipose tissue (WAT) is majorly composed of adipocytes. They function as endocrine and paracrine organs in addition to storing and metabolizing triglycerides to maintain energy balance. They secrete different factors that regulate angiogenesis, appetite, regulation of blood pressure, reproductive function, glucose metabolism, aging, immunological responses and inflammatory responses [1-3]. In mature adipocytes, cytoplasm is compressed to form a thin layer due to a large internal fat droplet and moving of nucleus to other edge of the cell [4]. Adipose tissues are formed due to accumulation of large number of adipocytes and form an insulting layer under the skin which regulates the body temperature. After reaching maturity, adipocytes become functional by highly controlled process known as adipogenesis [5]. Adipogenesis seems to be affected by Age, gender, and lifestyle in one way or another [6-8].

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Adipogenesis has been complemented with in depth research to understand characteristics of adipocytes. Adipogenesis is defined as the mechanism of cellular differentiation of fibroblast like pre-adipocytes into functional lipid containing adipocytes [Figure 1]. There are six roughly defined stages of adipogenesis including formation of mesenchymal precursors, commitment of pre-adipocytes, growth-arrest of pre-adipocytes, expansion of mitotic colonies, differentiation and maturation of adipocytes [1, 9]. Distinct morphological and molecular alterations occur in the pre-adipocytes to successfully transform into adipocytes.

Molecular Mechanism of Adipogenesis

The process of adipogenesis is extremely intricate mainly depends on interaction with surrounding tissue. Despite identification of several factors playing vital role in the process of adipogenesis, the detailed molecular mechanism is still unknown. Some of the key modulators of adipogenesis include fatty acids, growth hormone, prostaglandins, glucocorticoids, PPAR, STATs, SREBP1, C/EBPα, C/EBPβ, C/EBPδ, IGF-I, and macrophage colony stimulating factor [10-13]. Some additional regulators that affect the adipogenesis pathway have been reported by recent studies such as Krupel-like factors (KLFs), Wingless proteins (Wnts), B-cell factor 1 and GATA-binding

protein-2 and 3. Various cell cycle proteins, clock proteins and a number of interferon regulatory factors (IRFs) including IRF3 and IRF4 are also reported to impact abiogenesis [1, 14-18]. In addition, extracellular signaling proteins such as bone morphogenesis proteins, transforming growth factors, fibroblast growth factor, insulin like growth factor, notch ligands, pro-inflammatory cytokines and hypoxia discovered to have a significant impact on the adipogenesis process [6]. The series of events involving several of these molecules have been shown in Figure 2.

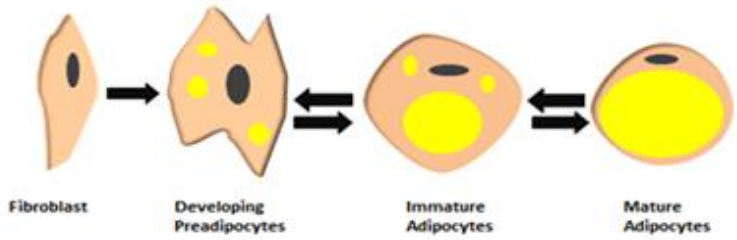

Figure 1: Stages of adipocytes differentiation. Reverse arrows showing shrinking of mature adipocytes in case of energy decrease.

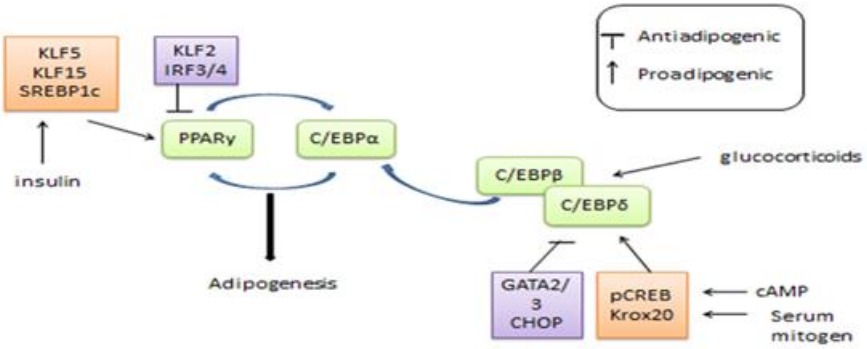

Figure 2: Transcription cascade of adipogenesis. Insulin and glucocorticoids are the factors that induce abiogenesis. These factors stimulate the regulation of various vital transcription factors that merge on PPARγ. PPAR then positively regulate the transcription of C/EBPα gene, and these factors collectively maintain differentiation of adipocytes.

Tumor-Microenvironment and Cancer

Tumorigenesis implicates continuous communication between Tumor-microenvironment (TME), immediate neighboring environment of a tumor and tumor cells. It has recently been suggested that TME through communication with the cancer cells supports the development of the hallmark characteristics which are required for tumor growth [19-22]. Without the complete explanation of TME, understanding of cancer is not possible. TME studies focus on the cancer-associated fibroblasts (CAF), their tumor promoting role [23] and the transformation of normal fibroblasts to CAFs through complex signaling pathways [24-25]. As pre-adipocytes are similar to fibroblasts and both originate from the same adipose stem cells (ASCs), therefore, functions of CAFs may explain adipocyte function as well [26]. Different studies have indicated that through adipokines or direct contact putative cancer associated adipocytes (CAA) near to cancer cell stimulates tumor growth. In benign adipose tissue, predominant cell type is adipocytes, other cell types such as vascular cells, fibroblasts, macrophages and precursor adipose cells are also present. Transition of benign fibroblast to a CAF speculates that all the cancer cells can recruit various elements of adipose tissue to enhance tumor growth and invasion. A number of studies suggest that in TME mature, differentiated adipocytes degenerate into pre-adipocytes to remove their large lipid droplet [27-28].

Tumor-Associated Adipocytes and Tumor Microenvironment

Tumor-Associated Adipocytes (TAAs) are the main residents of cancer microenvironments and are contributors of tumor growth by soluble factors like interleukin 6 or leptin. There is a strong crosstalk between tumor cells and TAA that plays an important role in tumor invasion [29-31]. Fatty acids occupy over 90% of adipocytes and their primary role is to provide energy for tumors. Tumor cells themselves promote lipolysis in the neighboring TAAs. The fatty acids release in this process triggers fatty acid oxidation in tumor cells that enhances the tumor aggressiveness [32]. It is predicted that the main

contributors in this process are TAAs associated extracellular vesicles allowing transport of nutrients to the distant cells. In obesity, more extracellular vesicles are secreted by adipocytes that transport proteins taking part in lipid metabolism such as fatty acid oxidation enzymes. It is not only protein machinery that is transported by these adipocytes derived extracellular vesicles but fatty acid substrates necessary for oxidation are also carried by extracellular vesicles [33-35].

Signaling Pathways Driving Adipocyte Lipolysis

Adipocytes maintain tissue homeostasis by releasing multiple endocrine factors such as adipokines, lipids mediators and extracellular vesicles. Studies showed that the interaction between the tumor cells and adipocytes secrete cytokines and adipokines. Interleukin-6 (IL-6) interacts with its IL-6R. This complex binds with gp130 on adipocytes which leads to the activation of Janus kinases (JAKs) and ultimately recruitment of transcription factors STAT1 and STAT3. The activation of STAT proteins moves to the nuclease which regulates the transcription of target genes such as *SOCS3* in adipose tissues. SOC3 impedes the insulin signaling pathway which drives lipolysis.

Tumor necrosis factor (TNF-α) also induces apolysis by interacting with its receptors on adipocytes. The binding of TNF-α with its receptors also causes the activation of JNK signaling pathway through TRADD, RIP1, and TRAF2 proteins. TNF-α downregulate the expression of phosphodiesterase-3B which increases the level of cAMP. cAMP activates the hormone sensitive lipase that causes the breakdown of lipids. The level of cAMP also increases by binding of β-adrenergic receptor with G-proteins

Tumor Cell Metabolic Adaptations for Fatty Acid Utilization

Tumor cells use fatty acid as alternative source of energy by remolding their metabolic pathways. CD36 is a lipid translocator protein that also activates STAT pathway. Tumor cells express high level of CD36 and FABPs proteins that enhance the cellular intake of fatty acids from adipocytes. Overexpression of CD36 protein causes the accumulation of lipid inside the cells that induce metastasis. Once fatty acids move into the cytosol, they are converted into the fatty acyl-CoA and undergo β-oxidation inside the mitochondria. Moreover, tumor cells also express high level of CPT1 (Carnitine Palmitoyl transferase 1) that increases the oxidation of fatty acid to meet the high energy demand for cell division. Low level of ATP also activates AMPK (AMP-activated protein kinase) pathway which increases PGC-1α gene expression. PGC-1α induces mitochondrial biogenesis and also increases the production of enzymes involved in fatty acid oxidation and oxidative phosphorylation. This enhances tumor survival and therapy resistance.

Crosstalk Between Mitochondrial Dynamics and Cell Migration

Mitochondria are organelle whose number and morphology depends on the metabolic state of cells. Tumor cells which are in contact with adipocytes undergo change in mitochondrial dynamics. Migration of tumor cells require mitochondrial fission which is achieved by Drp1 to supply the ATP and reactive oxygen species at leading edge. These ROS activate the ERK and FAK signaling pathways which are require for cell division and migration.

Tumor-Associated Adipocytes and Cancer Progression

TAAs together with extra cellular matrix constituents have emerged to contribute to tumor progression and invasion by producing a more supportive TME. Traditionally, adipose tissues act as energy reservoir in the form of triglyceride (TGs). These TGs release fatty acid when surplus amounts of energy are required. These TAAs not only produce energy but also provide protection for organs. However, in 1994, after discovery of leptin, adipose tissues were regarded as fully functional endocrine organ, having ability to regulate systemic energy and metabolic homeostasis [36]. A correlation between obesity and certain malignancies as endometrial and esophageal which have been demonstrated by epidemiological studies have further supported the notion of TAAs role in cancer progression.

Adipocytes are directly associated with tumor cells in many solid tumors during tumor proliferation, cancer cell infiltration and in hematological malignancies due to prevalence of adipose tissue in several organs. Over the last decade, studies relating adipocytes to tumorigenesis have increased with more focus on breast, ovarian, colon and prostate cancer. Adipocytes show profound functional and phenotypic alteration in stromal environment. In solid tumors histological images showed decrease in both cell size and cell number of adipocytes present at the invasive front as compared to adipocytes distant from the tumor [37-39]. In the tumor protruding region, the ratio of fibroblast-like cells becomes high due to de-differentiation of adipocytes because cancer cells release various signaling molecules [40].

Breast Cancer

TAAs have been reported to show their significant impact in breast cancer. Cell culture studies suggested that in serum restricted conditions, the co-culture differentiated murine 3T3-L pre-adipocyte cell line increases the tumor growth, metastasis, and survival of human breast cancer cell lines [41]. Conditioned-medium from differentiated 3T3-L1 cells supported

AP-1 transcription factors mediated invasion of cancer cells and NFκB and cyclin D1 mediated proliferation. Both adipocytes and fibroblasts contribute to proliferation of breast cancer cell lines, however adipocytes have significant impact on the division of cancer cells as compared to those of fibroblasts, lasting only a few days. Conditioned media release by adipocytes and fibroblasts induce similar survival transcriptional program but adipocytes influence the large number of genes and induce remarkable modifications as compared to fibroblast [42-43]. Studies conducted that conditioned-medium derived from primary human breast pre-adipocytes differentiated in culture promote the survival and proliferation of both normal and breast cancer cell lines [44]. However, the elements in the conditioned media that moderate this impact (growth factors, fatty acids, or reactive oxygen species) are unknown. A study reported that using differentiated murine 3T3-F442A pre-adipocytes increased invasiveness of the cancer cells in vitro providing evidence of establishing a crosstalk between adipocytes and breast cancer cells [45].

Prostate Cancer

Adipocytes have also a remarkable influence on the progression of prostate cancer. An adverse prognostic factor of prostate cancer is extra-capsular extension into peri-prostatic adipose tissue [46]. Adipocytes support tumorigenesis in highly differentiated, androgen-sensitive prostate cancer cell lines. Through the secretion of the MMPs peri-prostatic and visceral adipose tissue have a significant influence in progression and motility of prostate cancer cells [47-48]. Studies using FTIR spectroscopy reveal the transfer of lipid from adipocytes to prostate cancer cells that indicated adipocytes support prostate tumorigenesis [49-52].

Colon Cancer

Adipocytes also have a remarkable influence on the progression of colon cancer. Adipose tissue, mature adipocytes, or pre-adipocytes from leptin-deprived or wild-type induce the division of colon cancer cell lines in collagen three-dimensional collagen culture matrix. In every situation, the division of colon cancer cells was encouraged. Colon cancer cell proliferation was supported in all conditions. However, adipocytes provided leptin dependent proliferative effect. Mature adipocytes could not promote the growth of cancer cells in the absence of leptin, but this effect could be rescued by exogenous leptin treatment [53-56].

Ovarian Cancer

Ovarian cancer spread to omentum as primary human omental adipocytes induce the growth and metastasis of colon, breast, and ovarian cancer both in vitro and in vivo. Cytokines (IL-8 and IL-6) released by adipocytes cause the flow of ovarian cancer cells to the omentum. When ovarian cancer cells interact with adipocytes they induce hormone-sensitive lipase mediated lipolysis. These fatty acids release energy which are utilized by ovarian cancer cells. This was reported that ovarian cancer increases the β-oxidation of TGA which was suppressed by inhibitor, etomoxir. Etomoxir blocked the activity of enzyme carnitine-palmitoyl transferase 1 which inhibits the transportation of fatty acids into mitochondria and stops the growth of ovarian cancer cells. These high energy lipids from adipocytes support fast tumor growth by activating mitochondria metabolism. Lipid accumulation was also observed in colon and breast cancer cells which are cultured with adipocytes and metastatic human ovarian cancer tissue sections [57-59].

Clinical Significance and Therapeutic Implications of Adipocytes in TME

Tumor cells reprogram adipocytes into cancer associated adipocytes (CAAs) in TME. These CAAs secrete adipokines such as TNF-α and IL-6 that are correlated with tumor growth and metastasis. Therefore, these signaling molecules act as biomarkers for disease progression and increase metastasis. Moreover, high levels of lipolytic enzymes, lipid transporters and lipid binding proteins such as (CD36 and FABP4) also show the high lipid intake and tumor progression within adipocytes. Tumor metabolic state and treatment response can be detected by monitoring these changes in patients. Targeting the metabolic interaction between adipocytes and tumor cells can improve the chemotherapy induced apoptosis treatment. Tumor progression and invasion can also be reduced by targeting the adipokines, their receptors and lipid uptake pathways.

Conclusion

The current review highlights the role of TAAs in cancer mainly through regulation of TME by releasing several cytokines and lipids favoring cancer cells. These results suggest that by targeting TAAs and associated lipid metabolism, they may provide a potential paradigm to treat and prevent cancer progression. Moreover, the enzymes involved in regulation of lipolysis could be inhibited to stop cancer growth. Lifestyle interventions such as exercise and weight loss may be suggested to prevent cancer and enhance survival rates. The understanding of adipocytes effect in promoting cancer has greatly in past years, but some questions still need to be answered by further research. Despite these insights, the detailed mechanism of therapeutic exploitation of metabolic interaction between parasitic cancerous cells and host supportive TAAs will be required.

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