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T-Cadherin: A Missing Puzzle Between Cancer and Obesity

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Abstract

Obesity is a known risk factor for several cancers, with dysregulated cholesterol metabolism and altered adipokine signaling playing key roles in this association. T-cadherin (encoded by the CDH13 gene) is a cell surface receptor involved in mediating the effects of low-density lipoproteins (LDL) and adiponectin, two critical factors in obesity-related diseases. T-cadherin, lacking a transmembrane domain, is a unique molecular hub that both senses and modulates the effects of its ligands, regulating adipogenesis and lipid accumulation in adipose tissue. In this study, we explore the role of T-cadherin in adipocyte differentiation, using T-cadherin-deficient mice and mesenchymal stem cells (MSCs). We demonstrate that T-cadherin-deficient MSCs exhibit increased adipogenic differentiation and adipokine secretion, particularly adiponectin and leptin, while T-cadherin presence suppresses LDL-induced adipogenesis. Moreover, the downregulation of T-cadherin expression in various cancers suggests a potential tumor suppressor function, possibly through its involvement in adiponectin signaling and metabolic regulation. Our findings position T-cadherin as a crucial regulator linking obesity, adipose tissue homeostasis, and cancer progression, with implications for therapeutic targeting in obesity-related malignancies.

Keywords: Obesity; Cancer; Adiponectin; Cancer cells; T-cadherin; Mesenchymal stem cells; Adipogenesis

Mini Review

Obesity is recognized as a significant risk factor for various types of cancer. Particularly, obesity has been reported to be strongly linked with the following cancers: endometrial, esophageal adenocarcinoma, colorectal, postmenopausal breast, prostate, and renal, as well as leukemia, non-Hodgkin's lymphoma, multiple myeloma, malignant melanoma, and thyroid tumors [1]. However, there are various reasons potentially providing the rationale for this association. In cancer cells, the cholesterol uptake through the LDLR-mediated endocytosis pathway [2,3] along with enhanced cholesterol synthesis, contributes to abnormal metabolic processes. The cholesterol biosynthesis pathway has been identified as a promising therapeutic target, with several inhibitors demonstrating significant suppression of tumor growth and metastasis in various malignancies, including colorectal and pancreatic cancers [2]. Besides LDLR, several receptors mediate cholesterol uptake and adverse effects of low-density lipoproteins (LDL) [4], including T-cadherin [5]. As of today, T-cadherin is regarded as a multifunctional molecule involved in homophilic intracellular adhesion on the one hand and in intracellular signaling on the other.

Originally, T-cadherin was described as a cell-cell adhesion molecule [6], belonging to the family of "classical" cadherins that ensure organ and tissue integrity [7]. The extracellular part of T-cadherin, like the "classical" cadherins, consists of five extracellular domains [8]. Unlike the "classical" cadherins, T-cadherin lacks the transmembrane and cytoplasmic domains and is tethered to the plasma membrane via a glycosylphosphatidylinositol anchor, therefore, T-cadherin is involved in activating of intracellular signaling rather than in enabling strong homophilic adhesion [5]. However, besides homophilic interactions, T-cadherin operates as a receptor for two ligands - adiponectin and LDL, which are potentially competing to bind with this receptor in health and disease [5]. Adiponectin is a hormone produced by adipocytes in adipose tissue, exerts multiple protective effects in various tissues and cell types, including insulin sensitizing, anti-inflammation, anti-proliferation, and anti-atherosclerotic actions, as well as oncosuppressiion [9]. Plasma adiponectin content can be drastically reduced in metabolic syndrome [9-12], and T-cadherin becomes occupied by LDL, which are known to be elevated in obesity exerting their adverse atherogenic effects in cardiovascular

system [5]. The concept proposed in our lab views T-cadherin as a key regulator, acting both as a sensor and a switch to mediate either protective or detrimental effects based on its interactions with these two ligands and the consequent intracellular signaling pathways [5].

Some novel data have recently emerged indicating that T-cadherin can also be involved in adipocyte differentiation [13], whilst altered T-cadherin levels in adipose tissue and circulation can reflect the state of metabolic disorder [5]. To explore this in nuance, we utilized T-cadherin-deficient mice ($Cdh13^{\Delta Exon3}$ mice, which lack exon 3 of the Cdh13 gene encoding T-cadherin) previously generated in our lab. We evaluated the adipogenic differentiation potential of mesenchymal stem cells (MSCs) isolated from the adipose tissue of these mice compared to MSCs from wild-type (WT) mice. Our initial observations revealed that MSCs lacking T-cadherin (T-/- MSCs) were prone to spontaneous differentiation into adipocytes, forming large lipid droplets and exhibiting an increased adipogenic response to differentiating factors. Notably, T-/- MSCs displayed elevated baseline levels of PPARγ and CEBPα, which are the master genes driving the differentiation of preadipocytes into mature adipocytes [14,15]. Moreover, we detected a marked increase in both intracellular levels and the concentration of secreted adiponectin, a key marker typically associated with mature adipocytes [16]. The expression of adiponectin was evident from the early stages of adipogenic induction, with its levels progressively increasing over time and surpassing those observed in WT MSCs. Similarly, we observed an early onset of leptin synthesis and secretion, another critical marker of mature adipocytes [17]. These findings, coupled with the results from rescue experiments using lentiviral re-expression of T-cadherin in T-/- MSCs, indicate that T-cadherin-deficient cells exhibit a pronounced inclination for adipogenic lineage commitment, while T-cadherin acts as a restrictive factor in adipogenic differentiation.

To gain further insights into the role of T-cadherin in adipogenesis and to shed light on the potential function of T-cadherin in the adipose tissue, we performed a comparative study exploring the effects of LDL and adiponectin on adipogenic differentiation in relation to T-cadherin expression. Our results revealed the opposite effects of these two ligands: while LDL stimulated adipogenic differentiation, T-cadherin presence on the plasma membrane mitigated the impact of LDL on lipid droplet accumulation. Additionally, adiponectin treatment exerted suppressive effects on adipogenesis in WT MSC, while the lack of T-cadherin rendered T-/- MSCs more susceptible to these suppressive effects. These findings demonstrate that T-cadherin enables a differential feedback loop through interacting with its ligands. T-cadherin may potentially act as a sensor of systemic concentrations of LDL and adiponectin, thereby regulating adipose tissue homeostasis by guiding stem/progenitor cell differentiation into mature adipocytes and controlling lipid accumulation [16].

Over the past 30 years, mounting evidence has highlighted the significance of T-cadherin expression in various cancers. CDH13 gene, which encodes T-cadherin, is located on chromosome 16q24 - a region frequently exhibiting the loss of heterozygosity in different solid tumors. The downregulation of T-cadherin expression, triggered either by allelic loss of chromosome bands 16q24.1-q24.2 or hypermethylation of the CDH13 gene promoter, has been observed in numerous human cancers such as breast and lung carcinomas, pituitary adenomas, malignant B cell lymphomas and nasopharyngeal carcinoma [18- 22]. In osteosarcoma [23], ovarian cancer and endometrial cancer [24,25] as well as in gallbladder cancer [26] a decrease in T-cadherin expression was also linked with malignant phenotype and cancer progression. It has been proposed that T-cadherin may function as a tumor suppressor; however, no specific molecular or cellular mechanism has been definitively established so far.

As of today, circulating hormones and growth factors have been shown to directly influence tumor growth or indirectly impact cancer progression by modifying the stromal microenvironment (fibroblasts, immune or vascular cells) [27]. Adiponectin has gained considerable attention in cancer research, as emerging evidence correlates the low circulating levels of this adipokine with an increased incidence of obesity-linked cancers and higher mortality rates [28]. Notably, malignancies most often associated with low plasma adiponectin levels include digestive system cancers (esophageal adenocarcinoma, gastric, liver, and colorectal cancers (CRC)) or hormonally influenced cancers (post-menopausal breast cancers, endometrial, and prostate cancers) [28-31]. Studies in colorectal cancer cell lines further confirmed the growth-inhibitory role of adiponectin: in HCT116, HT29, and LoVo cell lines, adiponectin was shown to inhibit proliferation, migration and clonogenicity by modulating the cell metabolism as well as cell cycle [32,33].

Nevertheless, another group of studies have challenged the concept of adiponectin being a tumor suppressor. For instance, high levels of adiponectin were linked to an increased liver cancer risk in patients with chronic hepatitis C [34]. Furthermore, elevated adiponectin levels have been reported in pancreatic cancer [35]. Given the conflicting evidence on the role of adiponectin, it is crucial to consider the cellular and molecular mechanisms by which adiponectin may positively or negatively affect tumorigenesis. The reported discrepancies may suggest the role of adiponectin receptors rather than plasma adiponectin levels per se being crucial in cancerogenesis. For example, adiponectin receptors AdipoR1 and AdipoR2, both present on the plasma membrane in normal colon and human CRC samples [36], were elevated in tumor tissue, suggesting a compensatory mechanism to the diminished adiponectin plasma level [37]. The conceptual landscape in this field may change significantly, given the recent findings highlighting a strong correlation between CDH13 promoter methylation and the increased risk of CRC. Aberrant methylation of CDH13 promoter, which leads to downregulation

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of T-cadherin expression, has been identified as a potential diagnostic biomarker for the early onset of CRC [38]. Supporting this idea, our recent integration of bioinformatic analyses with immunohistochemical staining of human intestinal tissue from normal and CRC samples allowed us to specifically identify the cells that express T-cadherin (our unpublished data). In normal tissue, T-cadherin was predominantly expressed in mesenchymal stem/progenitor cells (MSCs) and endothelial cells. However, in CRC tissues, its expression decreased, remaining primarily in the endothelium. Notably, the cells expressing T-cadherin did not co-localize with those expressing ADIPOR1/ADIPOR2 (adiponectin receptors) or LDLR (a receptor for LDL) rendering T-cadherin expressing MSCs as endowed with a unique function.

To distill the vast complexity of putative roles that T-cadherin may serve, we suggest a concept of a molecular hub. First, T-cadherin regulates adipogenic differentiation of MSCs into mature adipocytes secreting adiponectin, thus overall affecting the systemic concentration of this adipokine in the blood stream. Second, T-cadherin acts as a sensor for systemic levels of its ligands, LDL and adiponectin, ensuring feedback loop and influencing adipogenic differentiation in health and disease. Third, T-cadherin may specifically operate as a receptor for adiponectin mediating its protective role against malignancy. In these roles, T-cadherin may be the missing puzzle between carcinogenesis and obesity.

Discussion

This study demonstrates the central role of T-cadherin in regulating adipogenesis and its potential involvement in cancer progression, particularly in obesity-related malignancies. Our findings reveal that T-cadherin deficiency in mesenchymal stem cells (MSCs) enhances adipogenic differentiation, with increased lipid accumulation and elevated adipokine secretion, including adiponectin and leptin. These observations suggest that T-cadherin normally acts as a restrictive factor in adipocyte differentiation, with its absence promoting adipogenesis. The differential effects of LDL and adiponectin on adipogenesis in T-cadherin-deficient MSCs further highlight its role as a sensor, balancing the actions of these two ligands to maintain adipose tissue homeostasis.

T-cadherin's involvement in cancer is also evident from our findings in colorectal cancer (CRC), where its expression is reduced, particularly in mesenchymal cells. The downregulation of T-cadherin in CRC suggests its potential role as a tumor suppressor, possibly by regulating metabolic pathways that impact cancer progression. The connection between low adiponectin levels and obesity-related cancers further supports T-cadherin's role in mediating adiponectin's protective effects against malignancy.

Conclusion

T-cadherin functions as a key regulator in adipogenesis and lipid metabolism, with significant implications for obesity and cancer. Its ability to modulate adipokine signaling and control adipocyte differentiation makes it a crucial player in metabolic homeostasis. Moreover, the loss of T-cadherin expression in cancer cells may contribute to tumor progression, underscoring its potential as a therapeutic target in obesity-associated cancers. These findings provide new insights into the molecular links between obesity, adipogenesis, and cancer, suggesting that T-cadherin could be a promising target for future diagnostic and therapeutic strategies.

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