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Chapter 1

STANDING OUT FROM THE CROWD: FUNCTIONS OF T-CADHERIN IN HEALTH AND DISEASE

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ABSTRACT

Cadherins are adhesion molecules which mediate homophilic Ca^{2+}-dependent intercellular adhesion. They play a crucial role in tissue morphogenesis during embryonic development and in the maintenance of tissue architecture in the adult. Cadherin-based adherens junctions and downstream signaling pathways are important for regulation of many processes during tissue remodeling such as cell sorting, polarity, migration, differentiation and survival. The cadherin superfamily is heterogeneous. Apart from the main large sub-families of structurally

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related members, it includes several atypical cadherins and cadherin-related proteins with unique molecular structures. Among these is T-cadherin (cadherin-13) which lacks transmembrane and cytosolic domains and is anchored to the plasma membrane *via* a glycosylphosphatidylinositol anchor. Due to the absence of an intracellular molecular moiety, T-cadherin-based intercellular contacts are weak and T-cadherin-dependent cellular processes are mediated by signaling mechanisms that are entirely different from those utilized by classical transmembrane cadherins. T-cadherin was originally described in the embryonic nervous system where it functions as a guidance molecule navigating projecting motor axons. Subsequently T-cadherin was demonstrated to regulate cell motility, proliferation, survival and phenotype of vascular endothelial and smooth muscle cells, cardiomyocytes, keratinocytes and several cancer cell types. Of particular interest is its function in angiogenesis and also its involvement in cardioprotective effects of adiponectin, an adipose tissue-derived hormone which regulates glucose and fatty acid metabolism and supresses progression of atherosclerosis. In the current chapter we review the existing knowledge and recent studies on T-cadherin structure, signaling, functions in different tissues, and relevance to pathogenesis of neurological disorders, cardiovascular disease and cancer.

ABBREVIATIONS

ADHD	attention deficit hyperactivity disorder
ADIPOQ gene	adiponectin gene
$AdipoQ^{-/-}$ mice	adiponectin knockout mice
Akt	AKT8 virus oncogene cellular homolog/protein kinase B
5-ALA	5-aminolevulinic acid
AMPK	AMP-activated protein kinase
APN	adiponectin
ApoE	apolipoprotein E
ASD	autism spectrum disorder
α-SMA	alpha-smooth muscle actin
BAL	bronchoalveolar lavage
BCC	basal cell carcinoma
CHD13 gene	cadherin-13/T-cadherin gene

Cdh13$^{-/-}$ mice	T-cadherin–knockout mice
CML	chronic myeloid leukaemia
COPD	chronic obstructive pulmonary disease
CRC	colorectal cancer
CVD	cardiovascular diseases
EC	endothelial cell
EC repeats	extracellular cadherin (EC) repeats
EGF	epidermal growth factor
EGFR	epidermal growth factor receptor
EMT	epithelial-to-mesenchymal transition
eNOS	nitric oxide synthase
ER	estrogen receptor
ERK1/2	extracellular signal-regulated kinase 1/2
GPI	glycosylphosphatidylinositol
GSK3β	glycogen synthase kinase 3β
GWAS	genome-wide association studies
HB-EGF	heparin-binding epidermal growth factor-like growth factor
HCC	hepatocellular carcinoma
HEK293	human embryonic kidney
IGF-1R	insulin growth factor-1 receptor
IGF	insulin like growth factor
IRS-1	insulin receptor substrate 1
LDL	low density lipoprotein
LOH	loss of heterozygosity
MAPK	mitogen-activated protein kinase
MEK	MAPK/Erk kinase
MMTV-PyV-mT model	mouse mammary tumor virus-polyoma virus middle transgenic model
MPs	microparticles
mTOR	mammalian target of rapamycin
NSCLC	non-small cell lung cancer
OSS	oral squamous carcinoma

p38 MAPK	p38 mitogen activated protein kinase
PCa	prostate cancer
PDGF	platelet-derived growth factor
PERK	protein kinase RNA-like endoplasmic reticulum kinase
PI3K	phosphoinositide 3-kinase
PpIX	protoporphyrin IX
Rac	Ras-related C3 botulinum toxin substrate
Rac1	Ras-related C3 botulinum toxin substrate 1
RhoA	Ras homolog family member A
S6K1	(p70) S6 kinase 1
SCC	squamous cell carcinoma
SMC	smooth muscle cell
TAC	transverse aortic constriction
TNFα	tumour necrosis factor alpha
VEGF	vascular endothelial growth factor
WT	wild type

1. Introduction

1.1. Cadherin Superfamily of Intercellular Adhesion Molecules

Cadherins play essential roles in important morphogenetic and differentiation processes during development, and in maintaining tissue integrity and homeostasis in adults. Cadherins mediate Ca^{2+}-dependent trans-junctional homophilic interactions at cell-cell interfaces that function to establish strong cell-cell adhesion and to define adhesive specificities of cells. The functions of cadherins extend beyond mere establishment of intercellular adhesion to multiple aspects of tissue organization and morphogenesis, including cell recognition and sorting, boundary formation in tissues, induction and maintenance of structural and functional cell and tissue polarity, cytoskeletal organization, cellular phenotype modulation, cell migration, cell proliferation and cell survival.

The cadherin superfamily is large and heterogeneous. It comprises more than 350 members found in various species; more than 100 members have been described in vertebrates [1]. According to the classification of Hulpiau and van Roy [2], which is based on an in-depth review and analysis of amassed data on molecular evolution and genomic sequencing, the superfamily is divided into two main branches, namely a cadherin major branch and a cadherin-related major branch. The cadherin major branch is comprised of two families C-1 (with type-I, type-II, desmocollins, desmogleins, 7D and solitary cadherin subfamilies) and C-2 (with Flamingo, type III and type IV cadherin subfamilies). The cadherin-related branch is subdivided into in four families: Cr-1a (protocadherins), Cr-1b (RET, FAT, Dachsous), Cr-2 (CDHR and μ-CDHR) and Cr-3 (FAT-like, CDHR28, CDHR15 and calsyntenins). The foremost common structural feature of cadherins is the presence of Ca^{2+}-binding extracellular cadherin (EC) repeats in their ectodomain, the number of these repeats varying from two in calsyntenins to 34 in FAT-like cadherins. While there are several conserved motifs in subsets of cytoplasmic domains, these domains are even more diverse than ectodomains [2]. Readers are referred to a range of excellent recent articles that variously review the evolution of cadherin family members, their diverse functions in tissue development and maintaining tissue integrity, and their many molecular mechanisms of action [3-28].

1.2. Distinguishing T-Cadherin from Other Cadherin Family Members: Structural Features

T-cadherin (cadherin-13, H-cadherin), which is encoded by the *CDH13* gene that is located on the chromosome 16q24 region [29], is a solitary subfamily member of the C-1 cadherin family [2]. T-cadherin is an atypical cadherin with several unique structural and functional characteristics. Its foremost distinctive feature is that it lacks transmembrane and cytoplasmic domains and is instead tethered to the plasma membrane by a glycosylphosphatidylinositol (GPI) anchor [30].

Another unique feature of T-cadherin is the structure of its relatively small adhesive pocket on EC1 domain, which has an isoleucine residue at position 2 instead of the conserved tryptophan residue in type I and type II cadherins [31]. Due to this amino acid substitution T-cadherin cannot mediate intercellular adhesion by formation of dimers through N-terminal EC1 domain interactions and "strand swapping" between partner molecules; instead T-cadherin forms X-dimer binding intermediates through an alternative non-swapped interface near EC1-EC2 Ca^{2+}-binding sites [15, 32]. T-cadherin has only a low Ca^{2+}-dependent homophilic-based adhesive capacity [31-33], and formation of mechanically stable cell-cell contacts is limited by the absence of cytoplasmic domain anchorage *via* armadillo catenins to the cytoskeleton. Moreover, T-cadherin is distributed diffusely over the cell surface with only mild enrichment in intercellular adherens junctions of quiescent cell monolayers, is primarily located on the apical surface of polarized cells, and undergoes redistribution to the leading edge of migrating cells [33-35]. Therefore, T-cadherin homophilic interactions are functionally more appropriate to dynamic adhesion-deadhesion processes than to strong intercellular adhesion.

1.3. Distinguishing T-Cadherin from Other Cadherin Family Members: Signaling Partners and Heterophilic Ligands

Another distinctive feature of T-cadherin concerns the mechanisms whereby it may trigger signal transduction. Other C-1 cadherin family members initiate signaling in the cytoplasm and nucleus through engagement of the intracellular domain with an assortment of intracellular binding partners (e.g., cytoskeletal regulators, protein kinases/ phosphatases, transcriptional cofactors) and lateral interactions of the transmembrane domain with growth factor receptors and other plasma membrane-located signaling molecules. However, due to its lack of transmembrane and cytoplasmic domains T-cadherin cannot trigger intracellular signaling *via* such direct engagement mechanisms. As demonstrated for other GPI-anchored proteins [36], T-cadherin-dependent

signal transduction necessarily requires some lateral interaction with accessory membrane molecular adaptors together with spatio-temporal reorganization of lipid rafts (where T-cadherin locates [37, 38]) and/or changes in T-cadherin protein clustering at the cell surface [39]. Investigations on molecular adaptors for T-cadherin are rare and restricted to endothelial cells (ECs): adaptors identified include insulin receptor, stress chaperone GRP78/BiP, integrin-linked kinase, GABA-A receptor α1 subunit, integrin β3, collagen α2 (I) chain and two hypothetical proteins, LOC124245 and FLJ32070 [40-42]. A fourth important distinctive property of T-cadherin relates to heterophilic interactions: it is the only member of the cadherin family for which a capacity for heterologous binding with any circulating or secreted ligand has been reported. Ligands identified to date include native low density lipoprotein (LDL) [43-46] and adiponectin (APN/ACRP30), an adipocyte-derived adipocytokine which is encoded by the *ADIPOQ* gene [47, 48]. Confocal microscopy, FRAP and FRET imaging *in vitro* using HEK293 cell line demonstrated that their respective ligation to T-cadherin occurs *via* distinct mechanisms. Native LDL binds to both 130 kDa prepro and 105 kDa mature T-cadherin proteins [45] and the GPI moiety of T-cadherin is necessary and sufficient for this interaction [49]. APN binds preferentially to 130 kDa prepro-T-cadherin protein and requires the region encompassing EC1-EC2 domains of T-cadherin [48], overlapping the region reported for homophilic *trans* interaction of T-cadherin [32]. Both LDL and APN binding to T-cadherin cause cell surface spatiotemporal organization of T-cadherin but in different modalities [39]. LDL induces rapid formation of short-lived T-cadherin clusters for which the presence of membrane cholesterol as well as an intact actin cytoskeleton are obligate, whereas T-cadherin cluster formation induced by APN is stable, independent of cholesterol, sensitive to actin perturbation and accompanied by internalization of T-cadherin [39].

Biochemical ligand-blotting techniques have identified LDL-T-cadherin binding interactions [44], but specific colocalization of LDL to T-cadherin in tissues/cell types *in vivo* has yet to be demonstrated. Direct physical association between T-cadherin and high molecular weight APN

has been demonstrated by co-immunoprecipitation experimentation using ECs, C2C12 murine myotubes and human embryonic kidney (HEK) cells [47, 50, 51]. APN colocalizes with cell surface expressed T-cadherin *in vivo* in a variety of tissues including the vasculature (on ECs and smooth muscle cells (SMCs) [35, 50, 52, 53], heart (on cardiomyocytes) [51, 52] and skeletal muscle (on myocytes, capillaries and larger blood vessels) [50, 52, 54]. Investigations in T-cadherin–knockout (*Cdh13*$^{-/-}$) mice have established that T-cadherin plays a crucial role in tissue accumulation of APN [35, 50-52, 54]. The pathophysiological relevance of interactions between T-cadherin and its heterophilic ligands in various tissues is discussed below in respective sections.

Cdh13$^{-/-}$ mice live well into adulthood without overt pathological phenotypes [35, 51], and identification of functions for T-cadherin *in vivo* have required challenging the mice in disease models. In the following we appraise current *in vitro* and *in vivo* knowledge regarding on T-cadherin expression and functions in different tissues and cell types and how it may participate in progression of many pathological conditions including cardiovascular diseases (CVD), neurological disorders and cancers.

2. The Nervous System

2.1. Axon Guidance

The development of functional neural circuits in the nervous system during embryogenesis and early postnatal period depends on a complex series of events involving axon guidance, axon and dendrite arborization, formation and maturation of synaptic structures, and elimination of unnecessary neural connections. Aberrant spatial and temporal orchestration of axon guidance processes have been linked to many neurological disorders [55]. Several types of structurally diverse molecules have been attributed a role in axon navigation and target recognition, among them semaphorins, netrins, slits, ephrins, cadherins, *inter alia*. The pioneering works of the group of Barbara Ranscht have not only identified

T-cadherin as a novel guidance molecule regulating pathfinding of projecting axons but also laid the foundation for the understanding of the principles underlying T-cadherin effects in other tissues.

In the chick embryo T-cadherin was suggested to be among the molecular cues which define migration routes of neural crest cells through somite-derived sclerotomes and maintain somite polarity. The assumption was based on the observation for differential expression of T-cadherin along the rostrocaudal axis of each sclerotome that coincided in time with the invasion of the first neural crest cells into the rostral parts of the somite and was increased towards the caudal parts of somites avoided by neural crest cells and extending axons [56]. Similarly, in the developing chick hindlimb muscle projecting motor axons avoided regions positive for T-cadherin expression which dynamically changed during initial extension of axons from the spinal cord, sorting into different nerve trunks and formation of terminal synapses in the muscle [57]. These data suggested that T-cadherin acts as a negative guidance cue to define trajectories of migrating neural crest cells and projecting axons. Direct evidence for this hypothesis came from *in vitro* studies which demonstrated that both T-cadherin substrata and soluble recombinant T-cadherin protein inhibited neurite growth through homophilic adhesion-dependent mechanism [58]. Immunohistochemical and knockout studies confirmed that T-cadherin contributes to axonal pathfinding by cortical projection neurons [59].

T-cadherin is likely to act in conjunction with other adhesion molecules to orchestrate formation of neural circuits. In the chick embryo T-cadherin and classical type I N-cadherin display alternative complementary expression patterns in nerve and muscle tissue [57], suggesting that combination of N-cadherin-dependent positive and T-cadherin-dependent negative navigation signals are necessary for correct wiring. In the chick optic tectum T-cadherin, N-cadherin and R-cadherin are expressed in distinct patterns during retinotectal synaptogenesis. Unlike the other two cadherins, T-cadherin is not concentrated at synapses and may play a role in limiting the arborization of retinal axons [60]. In the marmoset embryo cortical development appears to be coordinated by complex interplay between ten different cadherins including T-cadherin

which are differentially expressed at specific stages and areas of the developing brain [61].

2.2. Neuropsychiatric Disorders

The potential physiological role of T-cadherin in the development of neural circuits is highlighted by data from genome-wide association studies (GWAS) aimed at identifying candidate susceptibility genes for neurobehavioral and neuropsychiatric disorders. Variations in *CDH13* gene have been linked to the risk of substance use disorders such as nicotine dependence [62-64], alcohol dependence [65-68], methamphetamine and other illegal substance dependence [69-74] and altered response to amphetamine [75, 76]. *CDH13* has been reported to be expressed in the groups of neurons implicated in drug response, reward system and cognitive modulation such as the substantia nigra pars compacta and ventral tegmentum [77]. Animal studies demonstrate that *Cdh13*$^{-/-}$ mice display evidence for reduced reward from a normally highly rewarding cocaine dose. This effect is accompanied by alterations in dopamine levels, dopaminergic fiber densities and expression of the activity dependent transcription factor npas4 that regulates the excitatory-inhibitory balance within neural circuits [78]. *Cdh13*$^{-/-}$ rats displayed altered reward-directed behaviors, including cue-induced reinstatement of cocaine seeking [79]. Together, these data suggest that T-cadherin may regulate the activity of the dopaminergic brain system and dopamine-associated behavior.

Abundant evidence points to the importance of T-cadherin in the pathogenesis of attention deficit hyperactivity disorder (ADHD), a complex childhood behavioral disorder with environmental and genetic etiology that is characterized by inappropriate levels of attention, hyperactivity, and impulsivity. Among suggested pathophysiological mechanisms contributing to ADHD are connectivity disturbances in fronto-striatal or meso-cortical neural circuits and dysfunctions in the mesolimbic dopaminergic system [80]. In 2008 *CDH13* was identified as one of the top genes associated with ADHD [81] and since then confirmed to be a

potential risk gene for ADHD by many studies [82-87]. SNPs in *CDH13* gene were associated with alterations in neurocognitive functioning in ADHD patients [88], with risk tolerance and risk behaviors [89], and with extremely violent behavior in antisocial recidivistic offenders who frequently exhibit impaired impulse control and other ADHD symptoms [90]. *CDH13* variants have been also linked to autism spectrum disorder (ASD) which often shares traits with ADHD [91, 92], schizophrenia [93] and depression [66]. Mavroconstanti et al. performed sequencing of the *CDH13* gene in adult ADHD patients and healthy controls and attempted to characterize the identified *CDH13* variants by cloning and expression in CHO and HEK293 cells, but failed to detect any abnormalities in the processing or cellular localization of the mutant proteins (although effects on cellular functions such as neuronal migration have not been analysed) [94].

Significant progress has been made in understanding the mechanistic links between *CDH13* expression and the risk for neuropsychiatric disorders. Of particular interest are studies which utilize *Cdh13*$^{-/-}$ mice to study the role of T-cadherin in development of brain neural circuits. Analysis of the developing mouse brain demonstrates that in wild type (WT) mice *Cdh13* gene expression dynamically changes in the caudal-to-rostral direction and follows the trajectory pattern of serotonergic fibers. *Cdh13*$^{-/-}$ mice display increased density of 5-HT neurons in the dorsal raphe and higher serotonergic innervation of the prefrontal cortex. Since *Cdh13* gene is strongly expressed not only on 5-HT neurons but also on radial glial cells which play an important role in regulation of neuronal migration, these data suggest that T-cadherin regulates the development of the serotonergic system by participating in the spatiotemporal control of 5-HT neuron navigation [95]. Furthermore, T-cadherin is involved in the development of glutamatergic and GABAergic synapses [96] and negatively regulates hippocampal inhibitory GABAergic synapses, while its loss results in higher locomotor activity and alterations in learning and memory functions [97].

Interestingly, ADHD patients have been reported to have decreased serum APN levels, which are inversely correlated to psychiatric symptoms.

However, it is not clear whether adiponectin *per se* or its interactions with T-cadherin play any causative role in the pathogenesis of ADHD [98].

T-cadherin is also suggested to play a role in adaptation to stress and neuroprotection. *Cdh13*$^{-/-}$ mice exhibit decreased adaptive reactions caused by early-life stress leading to delayed habituation, no reduction of anxiety-like behaviour and decreased fear extinction [99]. T-cadherin deficiency was associated with altered endoplasmic reticulum function and expression of proteins involved in endoplasmic reticulum stress response including Grp78/BiP [99] which has previously been demonstrated to mediate T-cadherin signaling effects in the endothelium [100]. *Cdh13*$^{-/-}$ mice also exhibit an increased number of apoptotic cells and a concomitant decrease in amounts of interneurons and late-born pyramidal neurons in the cortex, thus pointing toward neuroprotective effects of T-cadherin during neuronal development [101]. Another study demonstrated that T-cadherin loss may contribute to cognitive and social behavioral deficits by affecting function of Golgi cells within the cerebellar cortex, which was evident from aberrant expression/localization of glutamate decarboxylase GAD67 involved in GABA synthesis and reduced spontaneous inhibitory postsynaptic current in Golgi cells in *Cdh13*$^{-/-}$ mice [102].

3. The Cardiovascular System

In vascular tissues T-cadherin is abundantly expressed on SMCs, ECs [43-46, 103, 104], pericytes and adventitial *vasa vasorum* [103]. It is not expressed on vascular adventitial fibroblasts *in vivo* [103]. In heart tissue T-cadherin is also expressed on cardiomyocytes [37, 51]. An increasing number of GWAS in human subjects have identified links between *CDH13* gene variants and blood pressure traits [105-108], blood lipid levels and composition [109, 110], coronary heart disease [111-114], ischemic stroke [115] and metabolic syndrome components [107, 112, 114-130]. Computational gene web analysis has also predicted that *CDH13* gene is vital to cardiovascular and metabolic diseases [131]. The effects of identified *CDH13* polymorphisms on expression, cellular distribution and

biological functionality of mutant T-cadherin protein in the various T-cadherin expressing cardiovascular cell types remain completely unknown.

3.1. Endothelial Cells and Angiogenesis

The endothelium is a multifunctional endocrine organ strategically placed between the vessel wall and the circulating blood, and is able to respond to physical and chemical signals by production of a wide range of factors that regulate vascular tone, cellular adhesion, thromboresistance, SMC proliferation, and vessel wall inflammation [132]. The endothelium is the principal regulator of vascular homeostasis and acute and chronic endothelial stress is a key event in many vascular pathologies [133, 134]. Endothelial dysfunction, activation and damage associated with lipoprotein oxidation and inflammation importantly contribute to initiation and progression of atherosclerosis. Pathological angiogenesis, a morphogenetic process resulting from abnormal activation of ECs, is a hallmark of advanced atherosclerotic plaques predisposing them to rupture and thrombosis, and also a characteristic feature of cancer contributing to growth of solid tumors and metastasis [133, 134].

Upregulation of T-cadherin on ECs occurs *in vitro* under conditions of oxidative stress [135], and *in vivo* during atherosclerosis [103] and restenosis [136] as well as on intratumoral neovascular ECs in murine tumor models of breast cancer, melanoma, lung cancer and rhabdomyosarcoma [137, 138] and in human hepatocellular carcinomas [139-141]. A large body of evidence supports that T-cadherin is capable of regulating several EC functions relevant to vascular protection/repair and control of angiogenesis. T-cadherin overexpression in ECs promotes cell cycle progression and proliferation [142] and protects against apoptosis induced by oxidative or endoplasmic reticulum stress [40, 135, 143], with transcription factor thioredoxin-1 being an important determinant of redox-sensitive regulation of T-cadherin in ECs [143]. Homophilic ligation of T-cadherin molecules by recombinant T-cadherin protein or agonistic antibody induces a more polarized, motile phenotype and promotes cell

migration [142, 144]. A consequence of T-cadherin ligation-dependent modulation of EC adhesive properties in a 2-dimensional monolayer culture system is induction of tubular structures and arrangement of ECs into multicellular interconnecting chains which form a capillary-like/networked pattern resembling the initial response of ECs to a pro-angiogenic environment [145]. Exposure of EC monolayer to preparations of endothelial-derived microparticles harboring T-cadherin on their surface (mimicking homophilic ligation) also induced EC arrangement into tubular angiogenic structures [146]. Use of 3D *in vitro* angiogenesis models (EC-spheroid and heart tissue) demonstrated increased active outgrowth of newly formed capillary-like sprouts following either upregulation of T-cadherin on ECs or homophilic ligation through embedment of spheroids/tissue in substrata containing recombinant T-cadherin protein [145].

Relevant *in vivo* functions for T-cadherin in angiogenesis/ revascularization have been demonstrated in murine models commonly used for investigating tumor development (the mouse mammary tumor virus (MMTV)-polyoma virus middle (pY-V-mT) transgenic model) (MMTV-PyV-mT) [35], peripheral artery disease (hind limb ischemia model) [50], cardiac hypertrophy (chronic pressure overload induced by transverse aortic constriction (TAC)) [51], and skeletal neovascularization (employing myoblast-mediated gene transfer into mouse skeletal muscle) [145]. In the mammary tumor model, T-cadherin gene ablation restricts tumor vascularization and expansion and also limits hypoxia-induced retinal angiogenesis [35]. In the hind limb ischemia model *Cdh13*$^{-/-}$ mice displayed impaired revascularization/blood flow recovery [50]. In the model of cardiac hypertrophy *Cdh13*$^{-/-}$ mice displayed reduced capillary density after chronic pressure overload [51]. Implantation of myoblast clones co-expressing VEGF and secreted T-cadherin protein induces formation of capillaries of larger diameters (without affecting vessel density) compared with respective clones expressing the same dose of VEGF alone. Importantly, clones expressing only T-cadherin protein affected neither density nor caliber of neovessels, suggesting that *in vivo* T-cadherin is not a primary angiogenic stimulus, but rather a modulator of

angiogenesis that requires initial destabilization of the vessel by growth factors (e.g., VEGF) in order to exert its actions on EC phenotype conversion, migration, proliferation and survival [145].

Intracellular signal effectors participating in T-cadherin-ligation-dependent modulation of EC angiogenic behaviors have been identified through *in vitro* studies, and include PI3K/Akt/mTOR/GSK3β pathway [41, 135], β-catenin [41], small GTPases RhoA and Rac1 [144], p38MAPK [135], and the protein kinase RNA-like endoplasmic reticulum kinase (PERK) branch of the unfolded protein response [147]. Domains EC1 and EC5 of T-cadherin were found essential for its proangiogenic effects [148]. Membrane proximal molecules with which T-cadherin can directly associate in order to initiate transmembrane signal transduction in ECs following T-cadherin engagement include stress chaperone GRP78/BiP, integrin-linked kinase and integrin β3 [40, 41]. An alternate model put forward for the proangiogenic properties of T-cadherin relates to the function of T-cadherin as a receptor for APN [35, 47, 50, 51, 149], the ability of APN to sequester a variety of growth factors/angiogenic cytokines [150], the essential requirement of T-cadherin for APN-mediated enhancement of angiogenic differentiation of ECs *in vitro* [50, 151] and for APN-mediated revascularization [50] and cardioprotection [51] *in vivo*. It has been hypothesized that T-cadherin-APN binding interaction on ECs enables T-cadherin to transmit transmembrane angiogenic signals through growth factors/angiogenic cytokines that are complexed with APN [35] or that APN signals through membrane proximal signaling molecules associated with T-cadherin (e.g., integrin linked kinase) [51].

Mechanisms whereby T-cadherin might co-opt or cross-talk with APN-associated factors to regulate angiogenic behavior are far from clear. APN has been shown to possess proangiogenic functions *in vitro* and *in vivo* and to promote activation of AMPK, Akt and eNOS [151]. APN-induced eNOS activation and functional responses to APN *in vitro* were abolished by transduction with either dominant-negative AMPK or dominant-negative Akt. Dominant-negative AMPK also inhibited APN-induced Akt activation, and PI3K inhibition or dominant-negative Akt inhibited eNOS activation and functional responses to APN without

affecting AMPK phosphorylation [151]. This study suggests that AMPK is upstream of Akt and that APN-induces angiogenesis by promoting cross-talk between AMP-activated protein kinase and Akt signaling within ECs. Although involvement of T-cadherin was not investigated in this study, the use of T-cadherin null mice demonstrated that APN requires T-cadherin to stimulate AMPK signaling [51]. Further, siRNA-mediated T-cadherin knock-down in ECs inhibits the ability of APN to promote migration and mitosis [50]. Since Akt axis signaling is a major transduction node activated in response to homophilic T-cadherin ligation in ECs [40, 41, 135] and homophilic ligation induces angiogenic responses even in the absence of APN [42, 145, 146], it is conceivable that APN might "piggy back" onto T-cadherin-ligation mediated PI3K/Akt/mTOR/GSK3β pathway activation. Whatever the mechanism, it can be assumed that heterophilic T-cadherin-APN interactions and homophilic T-cadherin-T-cadherin interactions and effects on intracellular signaling and cell function are not mutually exclusive; their independent functionality or interdependent cross-talk may depend on their relative expression levels under any given physiological or pathophysiological condition.

Another aspect of the role for T-cadherin in endothelial (patho)biology concerns its presence in the circulation as a component of EC-derived microparticles (MPs). MPs are small submicron plasma membrane-derived vesicles which originate from many cell types through exocytotic budding and shedding from cell membranes into blood and body fluids under physiological and pathological conditions [152-154]. They harbor biological information such as proteins (signal proteins and receptors, cytoskeleton and effector proteins), lipids, and nucleic acids, (e.g., microRNA, mRNA, DNA fragments) which can be transferred to proximal or remote cells (homologous or heterologous) without direct cell-to-cell contact. In addition to their biological actions in inflammation, immune responses and coagulation MPs are capable of directly stimulating intracellular signaling and eliciting cellular responses, such as proliferation, survival, adhesion, chemotaxis, and intercellular communication [152-154]. Endothelial-derived MPs are markers of endothelial dysfunction, and are considered to play a major biological role

in inflammation, vascular injury, angiogenesis, and thrombosis [155, 156]. *In vitro* studies have demonstrated that T-cadherin protein is present on MPs released from stressed/apoptotic ECs (exposed to TNFα, H_2O_2, or thapsigargin); these MPs can induce homophilic-ligation T-cadherin-dependent signaling (e.g., activation of Akt axis signaling) and a proangiogenic functional response in target ECs. In a study on young healthy individuals and a patient cohort characterized with respect to the stage of atherosclerosis and presence of endothelial dysfunction assessed by reactive hyperemia peripheral arterial tonometry, the presence of T-cadherin in plasma as a component of MPs was associated with endothelial dysfunction [146]. The level of T-cadherin harboring MPs was increased in patients with early atherosclerosis and with chronic coronary artery disease, and in these groups Spearman's correlation also revealed a significant dependency of T-cadherin release into the circulation and the degree of endothelial dysfunction. The presence of T-cadherin in plasma of patients with early atherosclerosis supports that upregulation and shedding of T-cadherin from ECs is an initial response of the endothelium to activation and stress.

3.2. Smooth Muscle Cells and Atherosclerosis

SMCs are the most abundant cell type in the blood vessel wall, and their primary function is to maintain vascular homeostasis through coordinated cycles of contraction and relaxation. Unlike the majority of cells in the adult organism which are terminally differentiated, vascular SMCs retain inherent plasticity even in the mature vessel and can undergo reversible changes in phenotype in response to changes in local environmental cues [157-161]. The differentiated SMC phenotype is characterized by expression of a unique repertoire of contractile proteins, myofilaments and signaling molecules necessary for regulation of smooth muscle contractility. The dedifferentiated SMC phenotype is characterized by decay of contractile markers and acquisition of synthetic, migratory and proliferative properties required for vascular development, reparation after

vascular injury and remodeling in response to altered blood flow. Deregulated SMC phenotype switching and failure to maintain/regain the differentiated state is a pathogenic basis for development of several vascular disorders such as atherosclerosis, post-angioplasty restenosis and hypertension.

Associations between altered expression of T-cadherin on SMCs and pathogenesis of occlusive vascular disorders have been reported in a number of studies. *CDH13* gene expression was found to be lower in porcine atherosclerosis-prone coronary arteries than in atherosclerosis-resistant mammary arteries [162], suggesting T-cadherin expression negatively associates with predisposition to atherosclerosis. However, several immunohistochemical and biochemical investigations rather support a positive association between T-cadherin expression and occlusive vascular disease. Increased T-cadherin expression was observed on intimal SMCs in the model of experimental restenosis during the early phase of reparative proliferation [136], in human aortic and coronary atherosclerotic lesions at different stages of disease progression [103, 104, 163], and also in cardiac allograft vasculopathy (with restenosis-like remodeling) and ischemic cardiomyopathy (with atherosclerosis-like remodeling) in a rat allograft model [164]. T-cadherin protein expression was also increased in aortic tissue from atherosclerotic apolipoprotein E (*ApoE*)-knockout mice as compared to that in WT mice [53]. Upregulation of T-cadherin transcript and protein expression in SMCs *in vitro* under different conditions of *in vivo* pathological stress (e.g., hyperglycemia, hyperinsulinemia, oxidative stress) [165] further supports elevation of T-cadherin on SMCs as a molecular component of occlusive vascular disease.

A role for T-cadherin in control of phenotype was initially suggested following immunohistological observations of upregulation of T-cadherin protein on SMCs in lesional arterial tissues from human atherosclerosis and experimental restenosis [103, 136], prominent inverse staining intensities for T-cadherin and SMC contractile marker alpha–smooth muscle actin (α-SMA) in diseased human aorta [103], and positive association between staining intensities for T-cadherin and proliferating

cell nuclear antigen [103, 136]. Subsequent gain- and loss-of function studies *in vitro*, variously using rat, porcine, murine and human aortic SMCs, provided direct evidence that T-cadherin is a molecular determinant of SMC phenotype. Overexpression of T-cadherin in SMCs prompts phenotype shifting toward dedifferentiation as manifested by loss of the typical differentiated “spindle” morphology, reduced filamentous actin/stress fibers and decay of differentiated SMC contractile markers (α-SMA, *sm*MHC and *h*-caldesmon) [166]. Further, T-cadherin upregulation altered abundance/cellular distribution of myocardin and myocardin related transcription factors [166], which are transcriptional coactivators of the serum response factor-dependent transcriptional regulatory program that critically controls SMC differentiation status [167-169]. Importantly, T-cadherin gene ablation *in vitro* enforced the morphological and contractile molecular signature of the differentiated phenotype [166], while a reduction in SMC T-cadherin expression accompanied transforming growth factor β1-induction of the contractile phenotype [53]. These findings indicate that although T-cadherin is ubiquitously expressed by SMCs in healthy vessels it is not essential for mature SMC contractile function but may rather play a permissive role with respect to control of direction and extent of SMC phenotype switching.

T-cadherin upregulation on SMCs *in vitro* is accompanied by several behavioral alterations consistent with SMC modulation to the differentiated phenotype and adoption of reparative/remodeling functions. These include the following: reduced intrinsic contractile competence [165]; increased rates of cell cycle progression and proliferation [166, 170]; reduced ability to adhere and spread on extracellular matrix substrata in association with an increased capacity for motility and directional/polarized migration [166, 171]; gain of matrix remodeling capacity manifested by collagen fibril reorganization in 3D-SMC spheroid cultures [165] and increased expression of matrix metalloproteinase 2 in monolayer SMC cultures [166]. Upregulation of T-cadherin also increases pro-survival autophagy [172], which has been proposed to serve as a major proteolytic mechanism to remove contractile proteins during phenotype transition to dedifferentiation and to be important to the development or maintenance of

the dedifferentiated phenotype [173, 174]. Molecular mechanisms and signal transduction pathways involved in mediating the many functions of T-cadherin in SMCs have been extensively reviewed [175, 176] and will only be outlined herein. PI3K/Akt is a major signal transduction node utilized by T-cadherin, with activation of GSK3β and mTORC1/S6K1 downstream effector branches [165, 166]. GSK3β inactivation is the dominant mediator of T-cadherin-induced dedifferentiation and proliferation [166]. Pro-survival autophagy depends on activation of MEK1/2/Erk1/2 pathway signaling [172]. Phenotype-associated functional transition from static cell anchorage (differentiated) to migration (dedifferentiated) involves adhesion molecule expression, cell-matrix adhesion, organization of intercellular contacts and control of intracellular tension forces generated by the actin cytoskeleton [177].

An unclear issue regarding the role of T-cadherin in SMCs is its putative function as a receptor for LDL, an established risk factor for atherosclerotic disease [178, 179]. Although LDL was identified as a heterophilic ligand for T-cadherin expressed in aortic medial tissue (i.e., predominantly composed of SMCs) almost 25 years ago [44-46], the physiological relevance of heterophilic LDL-T-cadherin interaction to vascular tissue remains very poorly defined. Ectopic overexpression of T-cadherin in HEK293, EA.hy926 and cadherin deficient L929 fibroblast cell lines enhanced LDL-induced signaling (intracellular Ca^{2+} mobilization, Erk1/2 MAPK and nuclear translocation of nuclear factor κβ) and functional responses (proliferation and migration) to LDL [180-182]. In SMCs LDL is capable of activating a number of intracellular processes variously linked to its ability to stimulate vasoconstriction or proliferation (e.g., intracellular Ca^{2+} mobilization, cytosolic alkalinzation, phosphoinositide turnover, activation of protein kinase C, S6-kinase and Erk1/2 MAPK, generation of reactive oxygen species, DNA synthesis, nuclear proto-oncogene expression, *inter alia*) [39, 183-188]. Establishing whether these responses of SMCs to LDL indeed involve direct T-cadherin-LDL binding interactions would require appropriate gain- and loss-of function in this cell type. Nevertheless, by analogy to the aforementioned data obtained through ectopic upregulation of T-cadherin

in other cell lines, one might speculate that T-cadherin-LDL binding can facilitate LDL-dependent vasoconstriction and mitogenic signaling.

3.3. Vascular Insulin Resistance

Expression of T-cadherin on ECs and SMCs is elevated *in vitro* under conditions of stress (e.g., oxidative, hyperglycemic, hyperinsulinemic) [135, 165], and *in vivo* in vascular disorders such as atherosclerosis [103] and restenosis [136] that are associated with insulin resistance. A relationship between T-cadherin expression on vascular cells and development of insulin resistance has been demonstrated, whereby T-cadherin upregulation or silencing respectively attenuated or enhanced insulin responsiveness. The effects of T-cadherin ligation on insulin sensitivity in vascular cells depend upon its ability to directly associate with insulin receptor within lipid rafts, and its utilization of PI3K/Akt/mTORC1 axis signaling and downstream targeting of components (e.g., S6K1, eNOS) common to insulin signaling [42]. Increased cell surface T-cadherin expression caused by oxidative stress, inflammation, or prolonged exposure to insulin results in chronic stimulation of the Akt cascade, which in its turn induces compensatory hyperactivation of the negative feedback loop of the insulin cascade leading to increased S6K1-mediated serine phosphorylation and degradation of insulin receptor substrate 1 (IRS-1), and subsequent attenuation of insulin signaling through IRS-1/PI3K/Akt [42, 165]. Insulin resistance in T-cadherin overexpressing ECs is functionally manifest as an attenuation of insulin-dependent eNOS phosphorylation and activation (i.e., reduced NO bioavailability), cell migration and angiogenesis [42]. These processes normally promote vascular quiescence and healing/ endothelial regeneration [189]. In T-cadherin overexpressing SMCs insulin resistance functionally results in a reduction in insulin-responsive contractile competence [165]. Insulin-induced IRS-1/PI3K/Akt axis signaling in SMCs is important to maintenance of the differentiated, contractile phenotype [190, 191]. Thus, although T-cadherin-dependent

activation of pro-survival/reparative pathways in vascular cells during initial stress or injury is advantageous to preserved vascular function [135, 172], in a setting of sustained stress chronic ligation of T-cadherin would compromise insulin-mediated vasculoprotective functions and exacerbate disease progression. *Cdh13*$^{-/-}$ mice have normal peripheral insulin sensitivity *in vivo*, based on hyperinsulinemic-euglycemic clamping (which measures glucose uptake) [192]. *Cdh13*$^{-/-}$ mice have not yet been examined for vasomotor sensitivity to insulin *in vivo*. However, based on *in vitro* observations of elevated levels of IRS-1 and enhanced insulin-dependent signaling in T-cadherin-silenced ECs and SMCs [42, 165] one may assume that insulin receptor/IRS-1 levels coupling and thus insulin sensitivity *in vivo* are at least intact.

Another effect of T-cadherin on vascular NO bioavailability, albeit independent of insulin, has been demonstrated in a study using *ex vivo* aortic ring segments from WT and *Cdh13*$^{-/-}$ mice [193]. T-cadherin gene ablation was associated with a reduction in basal tissue accumulation of NO and impaired vasorelaxation induced by acetylcholine (which increases endogenous NO). Aortic tissue homogenates from WT and *Cdh13*$^{-/-}$ mice exhibited comparable levels of phospho-eNOS^{Ser1177} indicating comparable eNOS activity. Reduced NO bioavailability was due to superoxide-mediated inactivation of NO and increased EC caspase 3 activity/apoptosis arising through suppression of Akt phosphorylation/activation. The impact of T-cadherin deficiency on Akt activity (reduced) and apoptosis (increased) in aortic tissue is consistent with *in vitro* studies demonstrating that Akt is a major signal target downstream of T-cadherin in vascular cells and that pro-survival properties of T-cadherin in ECs are mediated *via* Akt/mTOR and Akt/GSK3β signal pathways [41, 42, 135, 166].

3.4. Cardiomyocytes

T-cadherin is expressed on C2C12 myotubes *in vitro* and on cardiomyocytes *in vivo*, where it exhibits a globally punctuate distribution (in keeping with its location to lipid raft domains in the plasma membrane

[37]), and colocalizes with APN [51]. The physiological function of T-cadherin in cardiac tissue was investigated by examining myocardial responses of *Cdh13*$^{-/-}$ mice after TAC (which induces cardiac hypertrophy and heart failure) and after ischemia-reperfusion injury (which induces myocardial infarction) [51]. Myocardial responses to both short-term TAC (compensated hypertrophy, manifest as hypertrophy in association with normal contractility) and long-term TAC (decompensated hypertrophy, manifest as impaired contractility, increased ventricular dilation, reduced neovascularization and cardiomyocyte apoptosis) were exaggerated in *Cdh13*$^{-/-}$ mice. The response to ischemia-reperfusion injury, evaluated as myocardial infarct area and extent of apoptosis, was also exaggerated in the *Cdh13*$^{-/-}$ mice. The structural and functional responses of APN knockout (*AdipoQ* $^{-/-}$) mice to TAC and ischemia-reperfusion injury mice mirrored those of *Cdh13*$^{-/-}$ mice. Adenoviral administration of APN prior to cardiac stress prevented exaggerated hypertrophic and ischemia-reperfusion phenotypes and the associated reduction in *AdipoQ* $^{-/-}$ mice, but not in *Cdh13*$^{-/-}$ mice or in *AdipoQ* $^{-/-}$- *Cdh13*$^{-/-}$ double knockout mice. The presence of T-cadherin was also necessary for APN-dependent stimulation of AMPK [51]. In rats, volume overload induced by infrarenal aorta-vena cava fistula resulted in reductions in serum and myocardial APN levels, myocardial APN receptor (AdipoR1/R2 and T-cadherin) levels, and myocardial AMPK activity; dysfunction of ventricular myocytes isolated 12-weeks post fistula was demonstrated [194]. Thus, T-cadherin in conjunction with APN protects the heart from multiple stressors, such as chronically increased afterload and myocardial ischemia. How T-cadherin actually signals its cardioprotective contribution following sequestration of APN has not been delineated.

4. Lung

T-cadherin is expressed on pulmonary epithelial cells and pulmonary ECs [195]. Genetic variants of *CDH13* gene have been reported to determine Chinese individuals' susceptibility to chronic obstructive

pulmonary disease (COPD) [196]. Short-acting β2-agonist bronchodilators are the most common medications used in COPD, and based on the quantitative spirometric response to inhaled β2-agonists, genetic variants of *CDH13* determining bronchiodilator responsiveness have been identified [197]. An investigation on susceptibility to air pollution found that effects of particulate matter with an aerodynamic diameter ≤10μm on lung function decline was modified by *CDH13* genetic variants in Korean men [198]. T-cadherin have been demonstrated to downregulate surfactant protein D production in A549 lung cancer cell line with alveolar type-II cell characteristics *in vitro* [199]; however, physiological relevance of this phenomenon in bronchioloalveolar cells remained unknown.

Investigations on the functional role of T-cadherin in the (patho)physiology of lung function are limited and restricted to evaluating the relevance of T-cadherin as a receptor for APN. APN exerts beneficial effects on allergic airways responses [200], and available data suggests that T-cadherin may be important for APN transport into the lungs and for mediating some of the beneficial effects of APN on allergic airways responses. APN was lower in the bronchoalveolar lavage (BAL) fluid of naïve *Cdh13*$^{-/-}$ mice compared with that of WT mice suggesting a role for T-cadherin in transporting APN across the alveolar capillary barrier through a vesicular transcytosis pathway involving binding of APN to T-cadherin expressed on ECs [201]. However, after allergen (ovalbumin) or ozone exposure BAL APN concentrations were higher in *Cdh13*$^{-/-}$ mice [201, 202], indicating that, at least in the setting of lung injury/increased capillary permeability, diffusion/leakage of APN through paracellular pathways between ECs into the alveolar spaces rather than T-cadherin-mediated vesicular transport dominates movement of APN from the blood into the lungs. Compared with WT animals, *Cdh13*$^{-/-}$ mice exhibited reduced allergic airways disease inflammatory responses to ovalbumin sensitization and challenge as evidenced by a marked reduction in allergen induced airway hyperresponsiveness, eosinophil recruitment to the airways, Th2 cytokine expression, mucous cell hyperplasia and BAL IL-17A expression [201]. *AdipoQ*$^{-/-}$- *Cdh13*$^{-/-}$ double knockout mice reversed the effects of T-cadherin deficiency alone, indicating that T-cadherin did

not mediate the ability of APN to reduce allergic airways responses and that the protective effects of T-cadherin deficiency required APN [201]. It was suggested that effects of T-cadherin deficiency likely reflects activation of other APN signaling receptors/pathways (such as AdipoR1 or AdipoR2) secondary to elevated serum APN concentrations observed in *Cdh13*$^{-/-}$ mice [35, 50, 51, 201, 202]. In contrast to allergen challenge, APN binding to T-cadherin was found to be required for APN-suppression of ozone-induced inflammation: subacute ozone exposure inflammatory responses (IL-17A mRNA expression, terminal bronchiolar lesions, and *saa3* expression) were increased in *Cdh13*$^{-/-}$ mice and in *AdipoQ* $^{-/-}$ mice (vs. WT), but were not further increased in the *AdipoQ* $^{-/-}$- *Cdh13*$^{-/-}$ double knockout mice [202].

5. Pancreas

The islets of Langerhans are the functional units of the endocrine pancreas and have a paramount role in maintaining glucose homeostasis through regulation of insulin secretion. An important function for T-cadherin in regulating pancreatic insulin secretion has been identified by Tyrberg and colleagues [192]. In the pancreas T-cadherin localizes not only to the exocrine vasculature, but also to endocrine islet β-cells where it colocalizes with dense-core insulin-containing granules. *In vitro* comparison of the insulin-release properties of pancreatic islets isolated from WT and *Cdh13*$^{-/-}$ mice revealed that islets lacking T-cadherin expression exhibit a normal first rapid phase insulin release response whereas the second prolonged phase insulin release response was impaired, resulting in a 58% reduction of insulin secretion. *In vivo*, *Cdh13*$^{-/-}$ mice exhibit severely impaired or delayed second phase insulin secretion during hyperglycemic clamp. *Cdh13*$^{-/-}$ mice show normal islet architecture and insulin content, and a normal insulin sensitivity and glucose utilization in peripheral tissues, such as muscle. However, intraperitoneal glucose tolerance testing demonstrated that *Cdh13*$^{-/-}$ mice develop glucose intolerance, which may arise through inadequate insulin secretion [192]. In

addition to demonstrating the requirement of T-cadherin for sufficient and persistent glucose-stimulated insulin release by pancreatic β-cells, this study introduces a potentially novel function for T-cadherin in vesicular trafficking and exocytosis.

6. Liver

In normal liver samples, T-cadherin is expressed in ECs of large blood vessels and in myofibroblasts, weakly expressed in sinusoidal ECs, and absent in hepatocytes [140]. Hypomethylation of *CDH13* gene has been linked to liver cirrhosis [203]. Functional genomic screening identified T-cadherin as a molecule upregulated in liver-function-inducing stromal cells [204]. A role for T-cadherin in modulating hepatic functions has been explored [205]. Primary hepatocytes were cocultured with mock- or T-cadherin-transduced CHO cells on a substratum containing immobilized recombinant T-cadherin. Cellular or substratum presentation of T-cadherin to hepatocytes enhanced liver-specific functions as assessed by measuring albumin secretion, urea synthesis, and cytochrome P450 1A1 activity as surrogate markers for liver-specific protein synthesis, nitrogen metabolism, and detoxification functions. There are no further studies elucidating the role for T-cadherin in regulating hepatic phenotype.

7. Kidney

T-cadherin displays a distinct and dynamic expression pattern during the differentiation of foetal human glomeruli. At the early capillary loop stage it is expressed apically on visceral epithelial cells of Bowman's capsule which start to differentiate into podocytes, while at the advanced capillary loop stage it is restricted to the foot processes of the podocytes within the glomerular filtration barrier, suggesting a role in podocyte differentiation and the formation of the glomerular capillary network [206].

8. Bone and Cartilage

Microarray analysis has identified T-cadherin as a gene that might play a role in bone development and regeneration [207]. Downregulation of T-cadherin mRNA and protein was observed in chondrocytes from patients with knee osteoarthritis and suggested to contribute to the loss of protective effects of adiponectin in the osteoarthritic tissue [208].

9. The Cochlea

In the cochlea of postnatal and adult mice T-cadherin mRNA and protein were expressed in the organ of Corti, the spiral ganglion, and the stria vascularis. The protein was located apically on the inner and outer hair cells [209]. In rat cochlea T-cadherin was present in fibrocytes or pillar cells; its expression pattern was mutually exclusive with E- and N-cadherin and dynamically changed during embryonic development suggesting that it may regulate the emergence of specific cell phenotypes and cell differentiation [210].

10. Cancer

Cadherins are well recognized as key determinants of cancer progression. Epithelial-to-mesenchymal transition (EMT) characterized by downregulation of epithelial markers such as the prototype cadherin family member E-cadherin, with simultaneous upregulation of mesenchymal markers including N-cadherin, leads to malignant transformation and acquisition of invasive properties by carcinoma cells. *CDH13* gene is mapped to the chromosome region 16q24 which displays frequent loss of heterozygosity (LOH) in cancer suggesting a potential role for T-cadherin as a tumor suppressor. Indeed, inactivation of *CDH13* due to allelic loss or hypermethylation of the promoter region is frequently observed in solid

tumors. However, accumulating data from experimental studies suggest that T-cadherin-dependent regulation of cancer progression is a complex process which depends on the tumor type and involves both control of tumor cell function and cross-talk with the tissue microenvironment. Below we discuss the available data for T-cadherin expression and function in different types of cancer.

10.1. Cutaneous Cancer and Other Proliferative Conditions of the Skin

The epidermis, the most outward layer of the skin which protects the body from environmental factors, is a very dynamic tissue that undergoes constant turnover. Cell renewal in the epidermis is initiated by keratinocytes residing in the lower *stratum basale* layer which are mitotically active and possess stem cell-like properties. Daughter cells generated by basal keratinocytes detach from the basal membrane, move upwards, differentiate and create novel cell strata thus ensuring tissue renewal and regeneration. Keratinocytes are the predominant cell population in the epidermis, with other types including melanocytes, Merkel-Ranvier cells and Langerhans cells [211].

The relationship between T-cadherin expression and proliferative/ malignant disorders of the epidermis is a good example of complex and differential effects exerted by this protein on different cell types, even in the same tissue. The data from genetic association and immunohistochemical studies display significant discrepancies which might be attributed to heterogeneity of the analysed samples, cell and tumor types (as well as, possibly, to methodological issues such as the use of different antibodies).

In the healthy skin T-cadherin expression is strongest in the basal keratinocyte layer and gradually diminishes as new cells move upward to the skin surface and differentiate [212-214]. Since the cells in the basal layer exhibit the highest proliferation rates compared to their more differentiated descendants, this is the first indication that T-cadherin does

not necessarily act as a suppressor of keratinocyte proliferation. T-cadherin is also present in the basal layer of sebaceous glands, on myoepithelial cells of apocrine glands, in the secretory coils and excretory ducts of eccrine glands, on melanocytes [215], and in the skin stem cell niches of the hair follicle [214, 216].

In basal cell carcinoma (BCC), the most common type of skin cancer which originates from basal keratinocytes, LOH in intron 1 of the T-cadherin gene or aberrant methylation of the T-cadherin promoter region was found in 20% and 24% cases, respectively [217]. Decreased protein expression in tumor samples was also observed; however, another study reported the opposite, namely, strong upregulation of T-cadherin protein in BCC irrespective of the histological type including superficial, nodular and infiltrative morphology, with highest staining intensities at intercellular borders at the leading invasive fronts of the tumors [212]. While BCC progresses slowly and rarely metastasizes, squamous cell carcinoma (SCC) often shows aggressive behaviour with high metastatic potential. In contrast to BCC, SCC is characterized by hypermethylation of *CDH13* gene [218] and loss or aberrant expression of T-cadherin protein which correlates with histological features of hyperproliferative, poorly differentiated and invasive tumors [219, 220]. Common precursors for SCC include actinic keratosis and Bowen's disease which are considered low-risk and high-risk lesions for malignant transformation, respectively. T-cadherin protein is mostly retained in actinic keratosis although some regions displaying loss of expression in the basal layer of the epidermis have been shown to give rise to SCC tumors [219, 221]. In Bowen disease a markedly weakened expression of T-cadherin on the basal cell layer was observed [221]. Taken together, these data demonstrate T-cadherin downregulation plays a role in malignant transformation and progression of SCC but not BCC.

Experimental studies demonstrate that T-cadherin loss promotes proliferation, migration and invasion of keratinocyte and SCC cell lines *in vitro* [219, 222], as well as tumor growth and metastasis *in vivo* [223, 224]. Inhibitory effects of T-cadherin on SCC cells are likely to be mediated by regulation of epidermal growth factor receptor (EGFR) phosphorylation

and membrane compartmentalization, as well as modulation of cell-matrix adhesion through control of surface levels of β1 integrin [225-227]. Paradoxically, T-cadherin overexpression also stimulated growth of SCC tumors *in vivo*, which occurred *via* enhanced intra-tumoral angio/ lymphangiogenesis associated with increased VEGF expression by T-cadherin-overexpressing SCC cells [223]. This dual effect of T-cadherin on cancer progression was confirmed in studies on breast cancer (below).

T-cadherin expression is frequently lost in melanoma [215]. Downregulation of T-cadherin in melanocytes and melanoma cells promoted invasion, while re-expression inhibited anchorage-independent growth, migration, invasion, and tumor xenograft growth [215, 228, 229]. Inhibition of tumor growth by T-cadherin *in vivo* has been attributed to stimulation of apoptosis *via* attenuation of AKT/CREB/AP-1/FoxO3a signaling pathway [229]. *CDH13* gene expression in melanoma cells is under the control of transcription factor BRN2 which might participate in malignant transformation of melanoma by repressing T-cadherin levels in melanocytes [230]. Another study, however, demonstrated that T-cadherin may promote melanoma progression by recruiting stromal cell components to tumors [231].

T-cadherin expression in the basal keratinocyte layer is also decreased in psoriatic skin concomitantly with upregulation of P-cadherin which is considered to be a reflection of keratinocyte hyperproliferation in psoriasis vulgaris [232].

10.2. Breast Cancer

In the healthy breast tissue T-cadherin is expressed on the myoepithelium and on the mammary ductal epithelial cells where it displays a location on the apical surface of polarized cells characteristic for GPI-anchored proteins but not for classical cadherins [35]. Loss of T-cadherin expression attributed to aberrant *CDH13* promoter methylation, rather than to the presence of mutations in *CDH13* gene, was observed in human breast cancer cell lines, primary tumor tissue and metastases [233-

241]. The absence of T-cadherin expression occurred early during transition from premalignant lesions to invasive carcinoma [242], correlated with increased tumor size, lymph-vascular invasion, higher disease stage and poor prognosis in patients with axillary lymph node-positive breast cancer [243], with tumor grade and negative prognosis in triple-negative breast cancer [235, 244], with response to neoadjuvant chemotherapy for locally advanced breast cancer [245], and overall survival [246]. *CDH13* methylation was more prevalent in HER2-positive tumors [247, 248], correlated with estrogen receptor (ER) expression, and poor differentiation in ER-negative tumors was associated with decreased levels of *CDH13* gene expression [249]. The anti-tumor effects of cerivastatin in breast cancer cells were demonstrated to be accompanied by upregulation of T-cadherin expression [250].

Transduction of breast cancer cells with T-cadherin cDNA inhibited tumor growth and invasion *in vitro* and *in vivo* [233, 251]. Subsequent studies however demonstrated that, similarly to cutaneous carcinomas, the relationship between T-cadherin expression and breast cancer progression is complex and non-linear. The study of Hebbard et al. which utilized the MMTV-PyV-mT transgenic mouse model [35] demonstrated that T-cadherin expression was lost from developing mammary gland tumor tissue but was retained on ECs. Crossing the MMTV-PyV-mT model with *Cdh13*$^{-/-}$ mice demonstrated that T-cadherin deficiency reduced tumor growth by limiting tumor vascularization. However, at the same time it resulted in the appearance of a poorly differentiated tumor phenotype which actively metastasized to the lungs.

10.3. Prostate Cancer

CDH13 gene expression was reported to be decreased in prostate cancer (PCa) [252, 253]. Conversely, another study reported methylation of T-cadherin gene in only 31% of prostate cancers and in 20% of benign prostate disease [254]. Immunohistochemical analysis demonstrated that in contrast to gene expression levels which did not significantly correlate with

tumor progression, T-cadherin protein expression was drastically increased in early stages of cancer. Its expression was more prominent in organ-confined than in advanced hormone-resistant tumors, correlated negatively with the Gleason pattern and reflected luminal/basal differentiation cell status [255]. T-cadherin overexpression induced the loss of epithelial polarity in prostate cell line BPH-1 and metastatic PCa cell line DU145, promotes proliferation, invasion, 3D organoid growth and transmigration through EC monolayers by regulating activity of EGFR and insulin growth factor-1 receptor, and modulates PCa cell response to doxorubicin [255, 256]. In the prostate tissue *CDH13* gene expression is under control of androgens [252] and estrogen receptor ERβ [257] and contributes to acquisition of a basal stem cell gene signature [258, 259]. Together, these data suggest that T-cadherin expression dynamically changes during PCa progression and may differentially influence cancer cell behavior depending on the stage, differentiation and hormonal status of the tumor. Promoter methylation of *CDH13* has also been reported in the serum of patients with PCa and was associated with clinicopathological tumor features and prognosis [260, 261].

10.4. Lung Cancer

CDH13 gene was found to be often inactivated in lung cancer specimens and cell lines due to both promoter methylation and deletion of locus [262]. Most studies have demonstrated a relationship between the loss of *CDH13* gene expression and non-small cell lung cancer (NSCLC) [263-278, 279] where *CDH13* promoter methylation occurred more frequently compared with small cell lung cancers [234], reflected responsiveness of NSCLC patients to chemotherapy [280], and correlated with levels of folate [281] which has been implicated in chemotherapy response and the homeostasis of DNA methylation. Allelic frequencies of several SNPs located in *CDH13* gene promoter and intron regions were significantly associated with different pathologic stages of NSCLC [282]. *CDH13* gene was more hypermethylated in poorly differentiated NSCLC

than in moderately and highly differentiated tumors [283], in EGFR WT tumors as compared to those expressing EGFR mutations [284], as well as in adenocarcinoma as compared to SCC [285], correlated with invasiveness of lung adenocarcinomas [271], and was observed not only in tumors but also in plasma of NSCLC patients [286]. Data for relationships between loss of *CDH13* gene expression and overall survival of lung cancer patients are variable and have demonstrated correlation between poor overall survival and hypermethylation of *CDH13* gene [283, 284, 287, 288], between poor overall survival and hypermethylation of *CDH13* gene only in combination with *CDH1* gene hypermethylation [263], or no correlation between *CDH13* gene methylation status and survival [268, 270]. *Cdh13* gene hypermethylation has also been reported in animal models of spontaneous or carcinogen- and inflammation-induced lung tumors [289, 290] and facilitated local growth of transplanted NSCLC tumors in mice [265]. Frequent *CDH13* gene promoter methylation could be detected also in bronchial lavage of NSCLC patients [291]. Taken together, these data suggest that the loss of *CDH13* gene expression may serve as a diagnostic marker to detect early NSCLC.

10.5. Gastrointestinal Cancers

CDH13 gene methylation was observed in early Barrett's esophagus-associated neoplastic progression and in esophageal cancer [292-294], correlated with the stage and degree of tumor differentiation [295, 296], and clearly demarcated esophageal adenocarcinoma from esophageal SCC and normal esophagus [294].

LOH which includes the locus for the *CDH13* gene was demonstrated in gastric cancer tissues and was associated with lymphangial invasion of the tumors. Gastric cancer cell lines indeed displayed decreased levels of T-cadherin mRNA, although no mutations or abnormalities in the methylation status of the promoter region of *CDH13* gene were detected [297]. Another study, however, demonstrated abnormal methylation of the *CDH13* gene promoter in 35% gastric cancers independently of tumor

stage [293]. Reduced levels of T-cadherin mRNA correlated with larger tumor size, lymph node metastasis, invasion, poor differentiation and higher TNM stage [298], while high T-cadherin expression was associated with increased overall survival of gastric cancer patients [298-300]. Overexpression of *CDH13* gene in gastric cell lines resulted in cell cycle arrest, reduced colony formation, migration, invasion and metastasis. These effects were associated with increased E-cadherin, decreased vimentin levels and reduced Akt and mTOR phosphorylation suggesting that T-cadherin may prevent gastric cancer progression by preventing EMT transition and inhibiting the AKT/mTOR signaling pathway [300, 301].

Aberrant methylation of *CDH13* gene promoter has been detected in duodenal carcinomas [302] and colorectal cancer (CRC) cell lines and specimens including both advanced tumors and early adenomatous lesions [303-307, 308, 309, 310, 311] suggesting that inactivation of *CDH13* gene may play a role in malignant transformation of intestinal cells and multistage intestinal cancer progression. *CDH13* gene methylation correlated with poor differentiation [312] and predicted adverse overall survival in CRC [310, 313] but was more frequent in cancers which did not display metastasis to lymph nodes [314, 315].

APN has been suggested to exert anti-tumorigenic activities in different types of cancer [316]. While there is no direct evidence for pathophysiological importance of T-cadherin interactions with APN in cancer cells, APN has been shown to regulate T-cadherin expression in colon cancer cells [317], and CRC risk was significantly associated with genotypes displaying polymorphisms in both *CDH13* and *ADIPOQ* genes [318].

10.6. Liver Cancer

Expression levels and patterns of T-cadherin on ECs within hepatocellular carcinoma (HCC) tumors have been clearly linked to tumor stage and differentiation status [140], further emphasizing the role for T-cadherin in intratumoral angiogenesis. However, the data on expression

and functional effects of T-cadherin in HCC cells are variable. On the one hand and similarly to many other cancers, there is evidence for downregulation of *CDH13* gene expression in cancer tissue and HCC metastases due to genetic and epigenetic modifications [203, 319-322]. In contrast, another study reported that while little or no expression of *CDH13* gene was detected in four of five HCC cell lines, it was strongly upregulated in highly invasive Mahlavu cell line, as well as in approximately 50% of primary human HCC tumor specimens (*vs*. non-malignant liver samples) where it correlated with the loss of E-cadherin expression [323, 324]. Functionally, T-cadherin expression has been reported either to induce G(2)/M cell cycle arrest, inhibit cell proliferation and anchorage-independent growth and increase sensitivity to TNFα-induced apoptosis in HCC cells in a c-Jun-dependent manner [320], or to significantly promote motility and invasion without influencing proliferation [139] suggesting that T-cadherin upregulation with concomitant loss of E-cadherin may reflect EMT transition of HCC cells.

10.7. Pancreatic Cancer

Epigenetic modification of T-cadherin promoter was observed in pancreatic cancer cell lines and in 58% cases of primary pancreatic cancers. *CDH13* gene methylation was detected as early as in stage II cancer and in small tumors (less than 2 cm in diameter) suggesting that T-cadherin loss is an early event in pancreatic cancer progression [325].

10.8. Bladder Cancer

CDH13 gene methylation and/or downregulation of expression in different subtypes of bladder tumors, as well as in patients' serum were significantly associated with risk, high grade, invasion and unfavorable prognosis suggesting that T-cadherin may be a relevant diagnostic and predictive biomarker in bladder cancer [326-330].

10.9. Gallblader Cancer

T-cadherin was found to be specifically expressed in non-invasive foci of gallbladder cancer tissue, contrasting with the expression pattern of transcription factor Zeb1 which has been shown promote cancer cell invasion *via* repression of *CDH13* gene promoter activity [331]. Inhibitory effects of T-cadherin on gallblader tumor progression are mediated by downregulation of Akt3 expression and Akt phosphorylation, as well as through regulation of SET7/9-dependent stabilization of chromatin-bound p53 [332].

10.10. Gynaecologic Cancers

CDH13 gene deletion or hypermethylation of its promoter was reported in ovarian cancer [333-337], in hyperplasia and carcinoma of the endometrium [338, 339], and in cervical cancer [340]. Two studies evaluated potential biomarker value of CDH13 and CDH1 gene methylation in serum samples of cervical cancer patients. In the first, an aberrant methylation of the 5'-region of CDH1 or CDH13 genes in 43% of the patients which correlated with worse disease-free survival was demonstrated [341]. However, in another study a statistically significant higher frequency of DNA-methylation was demonstrated only for CDH1 gene, suggesting that CDH13 DNA-hypermethylation is not a good tool for cervical cancer screening due to low diagnostic specificity and sensitivity [342]. In cervical cancer garcinol was observed to exert tumor suppressive effects *via* T-cadherin-dependent activation of PI3K/Akt signaling pathway [343]. On the other hand, in uterine leiomyoma expression of T-cadherin was significantly higher than in adjacent normal myometrium and correlated with increased levels of basic fibroblast growth factor in tumor tissue [344].

10.11. Head and Neck Cancer

CDH13 gene methylation was detected in the sinonasal cancer [345], nasopharyngeal carcinoma [346] and head and neck SCC [347, 348]. Decreased T-cadherin mRNA expression correlated with advanced clinical stage, higher pathological grade, poor differentiation and worse progression-free survival in oral SCC [349]. T-cadherin overexpression inhibited proliferation of oral SCC cell lines through suppression of the PI3K/AKT/mTOR signaling pathway [349].

10.12. Tumors of the Nervous System

In neuroblastoma T-cadherin has been found to inhibit tumor growth by attenuating proliferative cell response to EGF [350]. *CDH13* gene is methylated in glioblastomas [351], and T-cadherin expression decreases during EMT transition and is linked to autophagy and invasion rates of glioblastoma cells [305, 352]. *CDH13* gene has been found to be a direct repression target of Long Non-Coding RNA H19-derived miR-675 which induces expression invasion of glioma cells [353]. Suzuki and co-authors reported an unexpected effect of T-cadherin that may be relevant for fluorescence-guided resection of gliomas [354]. 5-aminolevulinic acid (5-ALA) is metabolized to protoporphyrin IX (PpIX) that accumulates selectively in the tumor and exhibits strong fluorescence upon excitation, but glioma cells do not always respond to 5-ALA, which can result in incomplete or excessive resection. Fluorescence-negative glioma tumors had higher levels of *CDH13* gene expression, and T-cadherin negatively regulated the 5-ALA metabolic pathway since knockdown of *CDH13* gene in U251 glioma cells resulted in higher PpIX accumulation and enhanced fluorescence [354]. T-cadherin has been suggested to be involved in malignant transformation of astrocytes. Astrocytes from mice heterozygous or homozygous for a targeted mutation in the *Nf1* gene displayed increased cell motility and abnormal actin cytoskeleton organization concomitantly with upregulation of T-cadherin [355]. At the same time T-cadherin

induced growth arrest in astrocytes in a p21(CIP1/WAF1)-dependent manner [356]. Induction of p21 in response to T-cadherin-dependent contact inhibition has also been demonstrated in CHO cells [357].

10.13. Blood Cancers

CDH13 gene was frequently methylated in lymphoma [358, 359], chronic lymphocytic leukaemia [360], and in bone marrow from patients with acute myeloid leukaemia and chronic myeloid leukaemia (CML) [361]. Expression of T-cadherin mRNA was decreased in primary and blast crisis CML patients as compared with healthy controls and showed a negative correlation with the presence of BCR/ABL fusion gene [362].

10.14. Osteosarcoma

T-cadherin is present in osteosarcoma cell lines and is strongly expressed in primary and metastatic osteosarcoma lesions suggesting that it may promote osteosarcoma progression and metastasis [363-365]. Estradiol, progesterone and EGF are involved in transcriptional and post-transcriptional regulation of T-cadherin in cultured human osteosarcoma cells [365].

10.15. Pituitary Gland Tumors

Hypermethylation of *CDH13* gene was detected in pituitary adenomas where it correlated with invasive tumor phenotype and aggressive higher grade tumors [366, 367].

10.16. Retinoblastoma

LOH on chromosome 16q and specifically *Cdh13* gene has been reported in retinoblastoma [368]. Other studies, however, found no somatic mutations or differential *CDH13* gene expression between retinoblastoma and normal retina, thus suggesting that inactivation of *CDH13* is not likely to be the target of 16q loss in retinoblastoma [369, 370].

CONCLUSION

Abundant data supports the involvement of T-cadherin in a wide variety of (patho)physiological processes, from embryogenesis to cancer progression. The best elucidated functions of T-cadherin include axon navigation, regulation of angiogenesis and control of vascular and cancer cell proliferation, invasion and differentiation. In spite of recent significant progress and increased scientific interest in T-cadherin, the bulk of available data is descriptive, and experimental investigations which directly demonstrate cellular effects of T-cadherin remain scarce. This is especially true for signaling mechanisms mediating T-cadherin effects. The absence of transmembrane and cytoplasmic domains in T-cadherin molecule implies the existence of membrane adaptors which transmit the signals from the extracellular part of the molecule to its intracellular signaling targets. However, analysis of membrane interactions of GPI-anchored proteins is technically challenging. The presence of the lipid moiety renders these receptors highly dynamic and "promiscuous" allowing for fast movements between different membrane compartments and transient lateral interactions with various signaling partners. This property enables efficient functioning in processes requiring prompt cell responses to a changing microenvironment, such as navigation of polarized protruding structures, remodeling of cellular networks, or sensing the environment during directed cell invasion, *inter alia*. Functional outcome of these dynamic signaling events would highly depend on temporal and cellular states at the time of stimulation, as well as the complement of

membrane partners (including particular growth factor receptors) present in any given cell type. This is well-illustrated by the many cases of differential effects of T-cadherin in various tissues and contexts described in this chapter: for example, cell responses to T-cadherin-induced Akt axis signaling include stimulation of proliferation and migration of vascular ECs and SMCs but growth arrest of certain tumor cell types. Novel advanced analytical methods of cell biology and biochemistry are required to better understand the molecular machinery of T-cadherin-dependent signal transduction and to clarify the role for this atypical protein in pathogenesis of human diseases.

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