αT-catenin: A developmentally dispensable, disease-linked member of the α-catenin family

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ABSTRACT

α-Catenins are actin-filament binding proteins and critical subunits of the cadherin-catenin cell-cell adhesive complex. They are found in nominally-defined epithelial (E), neural (N), and testis (T) forms transcribed from three distinct genes. While most of α-catenin research has focused on the developmentally essential founding member, αE-catenin, this review discusses recent studies on αT-catenin (CTNNAL1), a developmentally dispensable isoform that is emerging as relevant to cardiac, allergic and neurological diseases.

Introduction

The cadherin-catenin complex is widely viewed as a linchpin of tissue cohesion and organization. This complex contains a transmembrane cadherin extracellular domain that engages an identical cadherin on adjacent cells. The cadherin cytoplasmic domain associates with catenins that either stabilize cell surface cadherins (e.g., p120ctn) or physically links cadherins to the underlying cytoskeleton (e.g., β-catenin and α-catenin to actin filaments; p120ctn to microtubules) to bring about robust intercellular adhesion.1-2 For historical reasons, the most well studied cadherin-catenin complex comprises cadherin and catenins typically found in epithelia across tissue types—an Epithelial-cadherin (E-cadherin), paired with the more ubiquitously expressed p120ctn, β-catenin and “epithelial” α-catenin (αE-catenin, or αE-cat). This “canonical” cadherin-catenin complex, however, belies known gene complexity at each protein position in the cadherin-catenin complex (Fig. 1). Although fundamental paradigms of cell-cell adhesion have been gleaned from this canonical cadherin-catenin complex, expansion of the cadherin-catenin gene family evolved for a reason— enabling cell and tissue specialization of the basic epithelial adhesive paradigm, which favors organismal fitness. In this review, we focus on one of the more recently evolved catenins, αT-catenin (αT-cat), as a means to understand how modest alterations in the cadherin-catenin adhesion system may be relevant to a range of human diseases.

α-Catenins: Knock-out phenotypes reflect tissue distribution

α-Catenins are β-catenin and actin-binding proteins, where binding to both β-catenin and actin is required to directly link the cadherin complex to cortical actin filaments. They are found in nominally-defined epithelial (E), neural (N), and testis (T) forms transcribed from three distinct genes,3 where each is sufficient to rescue cadherin-based adhesion in α-catenin-negative cell lines.3-6 As is often the case with early nomenclature, formal names can be misleading now that greater resolving RNA sequencing technologies are available. In this regard, the human genotype-tissue expression (GTEx) database7 clearly shows that αE-cat (CTNNAL1) is not epithelial-restricted, but rather ubiquitously expressed (Fig. 2a). These data are consistent with
evidence that mouse knock-outs targeting Ctnna1 across a range of tissues can lead to penetrant loss of cell-cell adhesion/tissue organization (e.g., whole embryo, skin, brain and heart). In contrast to the ubiquity of αE-cat, αN-cat (CTNNA2) is largely restricted to brain (Fig. 2b), consistent with evidence that Ctnna2 knock-out mice display hypomorphic brains and perinatal lethality. Remarkably, the more recently evolved αT-cat (CTNNA3), named after its expression in the testis and best known for its role in the heart, is also abundantly expressed in the brain, spinal cord, and peripheral nerve (Fig. 2c). Although Ctnna3 knock-out mice are viable and fertile, this curious tissue distribution of CTNNA3, together with growing linkages between CTNNA3 and diseases compatible with this distribution (see below), raise the intriguing notion that αT-cat/CTNNA3 may be the α-catenin most relevant to a broad range of human diseases.

αE-cat: Founding member of the α-catenin family

Due to its ubiquity, molecular and structural analyses are best known for αE-cat, the subject of recent excellent reviews. The prevailing view of αE-cat in the cadherin complex is as a mechanosensitive scaffold protein that features a series of six, bundled α-helical domain-regions. There are two key aspects to its mechanosensitivity. First, the C-terminal F-actin binding domain of αE-cat shows preferential binding to actin filaments under tension in vitro, suggesting that αE-cat may preferentially couple the cadherin/β-catenin complex to actin filaments that are under myosin-based cortical tension. Contractile actin structures are typically found at discreet plasma membrane locations (e.g., zonula and focal adhesions), and the precise nature of this force-activated binding event is presently unclear. Second, the middle or M-region of αE-cat undergoes force-dependent unfurling, exposing a cryptic site that favors recruitment of the related actin-binding protein, vinculin. In epithelia, vinculin recruitment to αE-cat occurs in regions of the plasma membrane that are under elevated forces, such as an apical adhesive zone known as the zonula adherens. Since a number of proteins interact with αE-cat through its mechanosensitive M-region, it is possible that some of these partners may be variably recruited to αE-cat under distinct force-activated thresholds (Fig. 3).

Given the level of amino acid identity/similarity between αE-cat and αT-cat (56.1%/73.7%) or αN-cat (76.5%/83.1%) (3), we may reason that these related α-catenins share an analogous mechanosensitivity. Although biochemical and cellular characterization of αN-cat and αT-cat lags behind αE-cat, recent studies suggest that cadherin complexes containing these α-catenins are indeed different. For example, αE-cat recruits vinculin to adherens junctions more effectively than αN-cat using an α-catenin negative epithelial cell line, possibly due αE-cat’s higher affinity for actin filaments in vitro. How such differences are leveraged by epithelia (αE-cat) and neurons (αN-cat) to suit their respective junction-coupling needs
Figure 2. α-Catenin isoform expression analysis across human tissues. Graphs exported from the human Genotype-Tissue Expression (GTEx) portal using CTNNA1, CTNNA2 and CTNNA3 gene identifiers. Expression values shown as Transcripts Per Million (TPM) calculated from a gene model with isoforms collapsed to a single gene. No other normalization steps were applied. Box plots are shown as median and 25th and 75th percentiles; points are displayed as outliers if they are above or below 1.5 times the interquartile range. Number of human tissue samples range from ~100-500 per tissue and can be viewed via the portal.
remains to be clarified. Moreover, in contrast to the established allosteric behavior of $\alpha$E-cat, where $\beta$-catenin binding curiously limits $\alpha$E-cat’s capacity to bind actin filaments in solution, $\alpha$T-cat can bind cadherin/$\beta$-catenin and actin filaments, simultaneously. Thus, while $\alpha$E-cat within the cadherin/$\beta$-catenin complex shows preferential binding to actin filaments under tension, $\alpha$T-cat behaves as a constitutively active, actin-binding protein that can physically couple cadherin/$\beta$-catenin to actin in the absence of tension, which may be relevant to $\alpha$T-cat’s unique junctional and tissue-specific role (see below). In addition to differences in actin-binding between $\alpha$E- and $\alpha$T-cat proteins, recruitment of ligand-binding partners through the M-domain also appears distinct, as loss of $\alpha$E-cat in heart reduces vinculin recruitment to cardiac cell-cell junctions, whereas loss of $\alpha$T-cat reduces plakophilin-2 (PKP2) recruitment (also below). Lastly, it is worth noting that all three $\alpha$-catenins show a capacity to form homodimers in vitro that are incompatible with cadherin/$\beta$-catenin binding, and which allows for robust F-actin binding and bundling activity. However, recently measured kinetic parameters suggest that only $\alpha$E-cat may be able to sustain the homodimeric state at physiological concentration in cells, where homodimerization contributes to membrane protrusive activities required for cell migration and nascent contact formation. Together, these data suggest that mechanosensor, M-domain-binding-partner and homodimerization abilities of $\alpha$T-cat are distinct from $\alpha$E-cat, which may be relevant to the tissue-restricted functions of $\alpha$T-cat.

**$\alpha$T-cat in the heart and cardiomyopathy**

$\alpha$T-cat was named for its localization in peritubular myoid cells of the testis, but is currently best known for its role in the heart. This is largely because $\alpha$T-cat null mice show no obvious fertility defects, but rather develop a dilated cardiomyopathy (DCM) after 3–6 months of age. Although mutations in $\alpha$T-cat have not yet been found associated with DCM in humans, two mutations (detailed below) have been implicated in the development of arrhythmogenic right ventricle cardiomyopathy (ARVC). As recent evidence indicates that the left ventricle is often affected in historically defined ARVC patients, this biventricular disease is now referred to as arrhythmogenic cardiomyopathy (ACM).

ACM disease is typically caused by mutations in proteins that comprise desmosomes, a type of cadherin-based intercellular adhesion that employs plaque proteins (plakoglobin, plakophilins, desmoplakin) to link to the intermediate filament cytoskeleton.
Desmosomes are particularly important in tissues that withstand substantial mechanical strain, such as heart and skin. In this regard, αT-cat prominently localizes to a specialized cell-cell junction in cardiomyocytes, known as the intercalated disc (ICD), which contains distinct adherens junction, desmosome and gap junction structures. In the hearts of higher vertebrates, the ICD largely comprises a hybrid adherens junction/desmosome structure known as the area composita, where this hybrid junction is considered optimized to withstand the increased mechanical load of the four-chamber mammalian heart.

Although the unique strength and molecular mechanics of this junction type remains poorly understood, αT-cat may be a key integrator of the area composita, as it directly binds the desmosome component plakophilin-2 (PKP2) while also participating in the cadherin/β-catenin complex, presumably reinforcing adherens junction and desmosome alignment (Fig. 4). Indeed, while αT-cat knock-out hearts develop normally due to compensation by the related αE-catenin, over time, these mice show reduced localization of PKP2 and the Connexin 43 gap junction component at intercalated disks. Reduced area composita, hybrid-junction coupling (via PKP2) likely contributes to the decreased cardiac contractility and ejection fraction of αT-cat null mice, whereas reduced gap junction coupling (via Connexin 43) increases sensitivity to ventricular arrhythmia following ischemic injury.

Evidence that PKP2 mutations are also associated with ACM, suggest that a particular aspect of αT-cat/PKP2 coupling may be important for normal right ventricle structure and function. For example, PKP2 interacts with αT-cat (but not αE-catenin) via the M-domain. As discussed above, both αE-catenin M- and actin-binding domains require force-dependent conformation regulatory events for their respective binding activities, whereas αT-cat appears less mechanosensitive, being more available to its binding partners. These or other differences may explain why αT-cat is dispensable for normal heart development (due to compensation by αE-catenin), but important for cardiac function with age. Indeed, as the mechanical load on the heart increases after birth and the ICD matures, αT-cat’s role as molecular integrator of the area composita appears critical, as evidenced by the earlier onset of cardiomyopathy in αT-cat mutant mice compared to αE-catenin conditional KO mice (3 versus 8 months of age, respectively).

Recent biochemical and cell culture studies now rationalize how αT-cat heterozygous mutations may function as dominant inhibitors of cardiomyocyte function in ACM: One mutation (V94D) blocks β-catenin binding and favors αT-cat homodimerization, leading to altered junctional localization in cardiomyocyte junctions; the second mutation deletes a leucine in the critical actin-binding domain (L765del) and induces protein dimerization/aggregation. Although formal evidence for these mutations causing ACM awaits testing in mouse models, it appears that both αT-cat pathogenic mutations enhance the intrinsic homodimerization and/or aggregation potential of αT-cat, which may prevent normal cadherin/catenin/actin coupling and other possible maladaptation.

Lastly, it is worth noting that requirement of α-catenin-based cell-cell adhesion to heart structure and function is not absolute, but contextual, and based on developmental timing or degree of tissue injury. For example, the early loss of both αE- and αT-cat in mice is incompatible with heart development but tolerated when induced perinatally. Remarkably, the loss of both catenins appears beneficial when removed in adult hearts subjected to ischemic injury, in part due to elevated YAP signaling that favors proliferation. Such complexities raise the counterintuitive possibility that attenuating the function of proteins collectively required for tissue development may be beneficial during adult tissue repair after injury.

αT-cat linkages to allergic disease

One of the more surprising developments in the α-catenin field are the number of independent genetic association studies linking αT-cat (CTNNA3) with asthma and food allergy. Genome-wide association studies have linked several non-coding CTNNA3 polymorphisms with two distinct forms of asthma, occupational asthma induced by chemical exposure and steroid resistant atopic asthma. One study identified copy number deletions in CTNNA3 associated with pediatric food allergy. The surprise with these associations is that the restricted distribution of αT-cat expression in human tissues (Fig. 2, brain/peripheral nerve, heart, skeletal muscle and testis) suggests that either rare, contextually activated or non-canonical cell-types contribute to allergic disease.

Using the viable and fertile αT-cat knock-out mouse described above, our team has validated these αT-cat linkages to asthma using both chemical and house dust-mite models of asthma. Curiously, full loss of
αT-cat strongly suppresses airway hyperreactivity, a hallmark of asthma, but the αT-cat-expressing cell type that drives allergic airway responses remains to be determined. Remarkably, the only lung cells that obviously express αT-cat are cardiomyocytes that line the pulmonary vasculature.\(^6^0,\,6^1\) However, anatomical differences in human versus rodent pulmonary veins, their proximity to airways and relative degree of cardiomyocyte ensheathment has raised doubt that cardiomyocytes are the αT-cat-expressing cell type that drives asthma.\(^6^1,\,6^2\)

An appealing cell-type to consider for linkages between an adhesion protein and allergic diseases are immune cells. Although low levels of αT-cat RNA have been detected in EBV-transformed peripheral blood cells and lymphoid cancer lines\(^5^4,\,5^6,\,5^8\) (https://www.proteinatlas.org/ENSG00000183230-CTNNA3/cell), evidence for protein detection is generally lacking, with exception of one study suggesting that αT-cat may contribute to the upregulation of basophil-activation markers, CD203c and CD63.\(^5^8\) Indeed, immune cells generally do not express cadherins or α-catenin adhesion components, but Th2-cytokines can robustly upregulate E-cadherin and αE-cat in dendritic cells and alternatively activated macrophages.\(^6^3-\,6^7\) We find no evidence that αT-cat is upregulated under these same conditions (not shown). Thus, future work will be required to further validate and understand these intriguing connections between αT-cat and allergic disease.
**αT-cat in the nervous system and disease**

Early studies documented αT-cat protein expression in brain, but functional significance of this expression has lagged presumably because of difficulties interrogating behavioral defects in mice. Moreover, identification of αT-cat-expressing cell types in the brain has been somewhat limited by the lack of robust tools (e.g., fluorescent membrane-anchored reporter mouse). For example, while an early study suggested that αT-cat protein may be expressed in murine cortical neurons, αT-cat is more prominently detected in ependymal cell junctions that line ventricles, as well as cells within the molecular layer of the cerebellum. In human tissue, RNA sequencing data reveal that αT-cat expression is highest in brain and spinal cord (Fig. 2), the latter of which is likely due to the presence of a central canal lined by αT-cat-positive ependymal cells. The unique functional role of αT-cat in this specialized epithelium remains unclear, however, as αT-cat knock-out mice show no obvious defect in ventricle structure, possibly due to compensatory upregulation of αE-cat.

Despite the absence of an obvious neurological phenotype in αT-cat null mice (Frans Van Roy, personal communication), a number of linkage studies raise the possibility that αT-cat may contribute to disease in humans. Specifically, the αT-cat gene, CTNNAA3, is located near a common fragile site on chromosome 10, and has been linked to late onset Alzheimer’s disease in females (reviewed in72). CTNNAA3 is also linked to autism in two large cohorts of European ancestry with replication in two other cohorts, and rare deletions in αT-cat were identified in individuals with autism spectrum disorder. While transcriptomic analysis of WT and αT-cat knock-out mouse cerebellum suggest alteration of pathways linked to Alzheimer’s and autism, future work will be required to define the cell type and unique junctional-specialization supported by αT-cat function. Indeed, available online transcriptomic datasets of human and mouse brain cell populations suggest that oligodendrocytes may be a major αT-cat-expressing cell type in brain.

**αT-cat associations with cancer**

Among the α-catenin family members, αE-cat is best appreciated for playing a contributing role in tumorigenesis in large part because it plays an integral part in epithelial cell-cell adhesion with E-cadherin (CDH1), a bona fide tumor-suppressor gene. Since αT-cat mRNA and protein are generally absent from epithelial tissues (Fig. 2; see also Human Atlas), there was an early expectation that it might not contribute to cancer. However, a number of recent studies suggest that we may need to keep an open mind on this front. For example, a recent proximity proteomics study revealed αT-cat as the 9th most abundant protein at E-cadherin contacts in non-transformed Madin Darby Canine Kidney epithelial cells, raising the possibility that low levels of αT-cat mRNA may be uncorrelated from its polypeptide abundance. Remarkably, CTNNAA3 is one of the largest genes in the genome (i.e., spanning 1.78 Megabases) and proximal to a common fragile site (FRAD10D). In this regard, monoallelic or reduced expression of CTNNAA3 is associated with urothelial carcinoma of the bladder, pancreatic cancer associated with Schwachman-Diamond Syndrome, oropharyngeal squamous cell carcinoma, and hepatocellular carcinoma. In addition, deletion, truncation and missense mutations were identified in CTNNAA3 in NSCLCs and laryngeal carcinoma. In some of these studies, αT-cat was knocked-down and phenotypes typically associated with cancer were modestly enhanced (e.g., proliferation, invasion, migration). Intriguingly, SNPs in CTNNAA3 were associated with radiation induced brain cancers and focal loss of CTNNAA3 was associated with a hybrid neurofibroma/schwannoma, perhaps consistent with the prominent expression of CTNNAA3 in brain and peripheral nerve (Fig. 2). While these studies are suggestive, future work that makes use of validated, isoform-specific αT-cat antibodies and αT-cat knock-out/floxed mice will be required to determine the extent to which αT-cat is a bona fide tumor suppressor protein, particularly since the relationship between cell-cell adhesion and cancer is not universally suppressive.

**Revised evolutionary perspective**

Comparison of the three α-catenin genes reveals that αT-cat is the most recently evolved, likely arising from an amniote-specific duplication of the αN-cat gene. Evidence that αT-cat emerged with the development of terrestrial vertebrates that have a four-chambered heart, together with it being linked to ACM disease and required for normal cardiac function during murine lifespan, has led to the notion that αT-cat evolved to address the unique mechanical demands of...
the heart. However, recent transcriptomic studies reveal that αT-cat is also abundantly expressed in the nervous system (Fig. 2). This not only strengthens the plausibility of recent genetic linkages between αT-cat and neurological diseases, but suggests that αT-cat evolved to meet the demands of two very different tissue systems (i.e., brain/peripheral nerves and heart). The mechano-organizational features that αT-cat uniquely brings to adherens junctions across these systems will require further study. Thus, while most of α-catenin research has focused on the developmentally essential founding member, αE-cat, the developmentally dispensable αT-cat may be worthy of greater attention, emerging as a broadly disease-relevant α-catenin.

Disclosure of potential conflicts of interest
No potential conflicts of interest were disclosed.

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