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Fortilin, A Potential Target for the Prevention and Treatment of Human Diseases

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Abstract

Fortilin is a highly conserved 172-amino-acid polypeptide found in the cytosol, nucleus, mitochondria, extracellular space, and circulating blood. It is a multifunctional protein that protects cells against apoptosis, promotes cell growth and cell cycle progression, binds calcium (Ca^{2+}), and has anti-pathogen activities. Its role in the pathogenesis of human and animal diseases is also diverse. Fortilin facilitates the development of atherosclerosis, contributes to both systemic and pulmonary arterial hypertension, participates in the development of cancers, and worsens diabetic nephropathy. It is important for the adaptive expansion of pancreatic β -cells in response to obesity and increased insulin requirement, for the regeneration of liver after hepatectomy, and for protection of the liver against alcohol- and ER stress-induced injury. Fortilin is a viable surrogate marker for in vivo apoptosis, and it plays a key role in embryo and organ development in vertebrates. In fish and shrimp, fortilin participates in host defense against bacterial and viral pathogens. Further translational research could prove fortilin to be a viable molecular target for treatment of various human diseases including and not limited to atherosclerosis, hypertension, certain tumors, diabetes mellitus, diabetic nephropathy, hepatic injury, and aberrant immunity and host defense.

Keywords

Fortilin; translationally controlled tumor protein; TCTP; histamine-releasing factor; HRF; TPT1; apoptosis; atherosclerosis; hypertension; pulmonary arterial hypertension; diabetes mellitus; alcohol liver injury; endoplasmic reticulum (ER) stress; IRE1 α ; liver regeneration; development; host defense; immunity; tumors; cancers

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1. INTRODUCTION

Fortilin—also known as translationally controlled tumor protein (TCTP), histamine-releasing factor (HRF), and tumor protein translationally controlled 1 (TPT1)—is a 172-amino-acid multifunctional protein that exists in the cytosol [1], nucleus [1], mitochondria [2], extracellular space [3], and circulating blood [4]. Dimethyl sulfoxide (DMSO) causes mouse erythroleukemia (MEL) cells to halt the translation of several mRNAs as the cells undergo erythroid differentiation. Yenofsky and coworkers reported in 1983 that two mRNA species coding for 40 and 21 kDa proteins (p40 and p21) accumulated as translationally inactive messenger ribonucleoprotein particles—separate from translationally active polysomes—in the cytosol of DMSO-challenged MEL cells [5]. Chitpatima and coworkers from the same laboratory cloned the p21 protein and reported its sequence in 1988 [6], and Gross and coworkers cloned its human ortholog in 1989 and reported it as *a* translationally controlled human tumor protein [7]. Researchers subsequently began to use TCTP as the proper noun for the p21 protein, although there are many translationally controlled proteins and the molecule is known to be under the control of multiple transcription factors [8] and is expressed in both normal and tumor cells [1]. Some researchers refer to the molecule as HRF because it causes basophils to release histamine in an IgE-dependent fashion [9–11]. Herein we use the term *fortilin*^{TCTP}. Fortilin comes from the Latin *fortis* (strong and robust) and is appropriate for the anti-apoptotic/pro-survival [1, 2, 4, 12–28], pro-growth/proliferative [29–39], calcium (Ca²⁺) scavenging [17, 40, 41], and anti-pathogen activities [42–54] reported for the molecule.

Despite its diverse functions, *fortilin*^{TCTP} is best known for its anti-apoptotic role, which has been extensively validated in cellular [1, 16, 17, 22, 55] and whole animal [12, 13, 20] systems in both overexpression [1, 12, 14, 16] and knockout [1, 14, 16, 17, 56] experiments using various noxious stimuli including and not limited to etoposide [1], 5-fluorouracil [16], calcium [17], and oxidative stress [22, 55]. Mechanistically, *fortilin*^{TCTP} exerts its anti-apoptotic activity through multiple pathways. First, *fortilin*^{TCTP} binds to the tumor suppressor protein p53. The binding both destabilizes p53 [24] and prevents p53 from transcriptionally activating proapoptotic molecules such as B-cell lymphoma 2 (BCL2) Associated X Protein (BAX) [14]. *Fortilin*^{TCTP} also represses transcription of p53 itself and promotes mouse double minute 2 homolog (MDM2)-dependent degradation of p53 [27]. Second, *fortilin*^{TCTP} collaborates with BCL2 family proteins to inhibit apoptosis: *Fortilin*^{TCTP} binds myeloid cell leukemia 1 (MCL1), an anti-apoptotic BCL2 family protein [26], and stabilizes it [21]. *Fortilin*^{TCTP} also binds and enables BCL2-like 1 (BCL-XL), another anti-apoptotic BCL2 family protein, to protect against apoptosis [25]. In addition, *fortilin*^{TCTP} is inserted into the mitochondrial membrane and prevents BAX from dimerizing and inducing mitochondrial outer membrane permeabilization (MOMP) [2]. Third, *fortilin*^{TCTP} binds Ca²⁺, scavenges and sequesters it intracellularly, and protects cells against Ca²⁺-dependent apoptosis [17].

Another important biological role of *fortilin*^{TCTP} is its positive regulation of the mechanistic target of rapamycin (mTOR) signaling pathway. In response to various intracellular and extracellular cues, the pathway regulates organismal growth and homeostasis [57]. mTOR is a serine/threonine protein kinase, and it binds raptor and other proteins to form mTOR

complex 1 (mTORC1). Raptor binds mTOR substrates such as 4E-BP1 and p73S6K, presenting them to mTOR to be phosphorylated [57]. Rheb is a 184-amino-acid, 21-kDa polypeptide and exists in either active GTP-bound (Rheb:GTP) or inactive GDP-bound (Rheb:GDP) form. Rheb:GTP, but not Rheb:GDP, binds mTOR and stimulates its protein kinase activity [58]. The tuberous sclerosis complex (TSC1/2) is a specific GTPase-activating protein (GAP) for Rheb and facilitates the conversion of active Rheb:GTP to inactive Rheb:GDP. Hsu and coworkers, in their genetic studies using *Drosophila*, showed that fortilin^{TCTP} binds Rheb and functions as a guanine nucleotide exchange factor (GEF) for the molecule [34], and this finding also was supported by the work of Dong and coworkers [59]. GEFs stimulate the release of GDP from the protein to allow it to bind GTP and then facilitate the conversion of inactive Rheb:GDP to active Rheb:GTP [57]. Although the physical interaction between fortilin^{TCTP} and Rheb has been questioned by two independent groups [60, 61], Le and coworkers showed that intact 14-3-3 proteins are required for fortilin^{TCTP} to bind Rheb [35], suggesting that the status of 14-3-3 proteins could have potentially contributed to the failure to reproduce fortilin^{TCTP}–Rheb interaction data [60, 61]. Despite the controversy about the mechanism of action [60, 61], phenotypic and genetic studies using *Drosophila* and *Arabidopsis thaliana* support the premise that fortilin^{TCTP} increases cell size, cell number, and organ size, most likely through activation of the mTOR cell growth and proliferation pathway [34, 35, 62, 63].

In addition to basic biochemical and molecular biological characterization of fortilin^{TCTP}, an increased number of reports on the roles of fortilin^{TCTP} in the developmental abnormalities and diseases of humans and animals have been published in recent years. Because many excellent reviews have been published about its molecular and cellular biology [55, 64–68], here we will focus on the involvement of fortilin^{TCTP} in human and animal pathophysiology and explore fortilin^{TCTP} as a molecular target of human diseases (Figure 1).

2. FORTILIN^{TCTP} IN HUMAN DISEASES AND DEVELOPMENTAL ABNORMALITIES

2.1. Atherosclerosis

Atherosclerosis is the thickening of the inner most layer of the arteries (or the intima), which lead to heart attack, stroke, intermittent claudication and limb loss, and abdominal aneurysm formation. Endothelial cells (ECs), macrophages (MΦs), and vascular smooth muscle cells (VSMCs) play a vital role in the development of atherosclerosis. In the early stages of atherosclerosis, low density lipoprotein (LDL) particles in the plasma diffuse into the subendothelial space through the EC layer, which experiences an altered barrier function, are retained by the extracellular matrix, and are oxidized to become oxidized LDL (oxLDL). oxLDL is cytotoxic, proinflammatory, chemotactic, and proatherogenic [69]. oxLDL recruits circulating monocytes into the intima, where they differentiate into MΦs. MΦs internalize oxLDL through their scavenger receptors [70] and turn themselves into foam cells (FCs) that contain massive amounts of cholesteryl esters in their lysosomes. FCs proliferate in response to mitogens in the microenvironment, secrete proinflammatory cytokines and chemokines, and attract more monocytes to the intima, thereby magnifying the inflammatory response in a vicious cycle of atherosclerogenesis [69, 71, 72].

Mice lacking both the LDL receptor (Ldlr) and apolipoprotein B mRNA editing enzyme catalytic polypeptide 1 (Apobec1) genes (denoted Ldlr^{-/-}Apobec1^{-/-} mice hereafter) constitute a robust mouse model of human familial hypercholesterolemia and develop severe atherosclerosis on normal chow diet within the several months of their lives [73]. In both the aorta of these mice and human atherosclerotic tissue samples obtained from carotid endarterectomy, fortilin^{TCTP} was found to be abundantly expressed in the atherosclerotic intima, and its expression was positively correlated with the degree of atherosclerosis and temporospatially coincided with MΦs and FCs [23]. To test the hypothesis that fortilin^{TCTP} facilitates atherosclerosis, we generated fortilin^{TCTP+/+}Ldlr^{-/-}Apobec1^{-/-} and fortilin^{TCTP+/-}Ldlr^{-/-}Apobec1^{-/-} mice. We could not use fortilin^{TCTP-/-} mice because they are embryonically lethal as we [20] and others [2, 13] reported. We have exclusively used Ldlr^{-/-}Apobec1^{-/-} mice [74] because they represent the most scientifically rigorous model of human familial hypercholesterolemia with markedly elevated LDL levels [73, 75]. Although the total cholesterol level of apolipoprotein E (ApoE)^{-/-} mice is comparable to that of Ldlr^{-/-}Apobec1^{-/-} mice (~560 [mg/dL]) and both strains develop robust atherosclerosis on normal chow [73], most of the cholesterol in ApoE^{-/-} mice resides in very low density lipoprotein (VLDL) and chylomicron (i.e., not in LDL). In contrast, most of the cholesterol in Ldlr^{-/-}Apobec1^{-/-} mice resides in LDL [73]. ApoE deficiency was also shown to result in defective phagocytosis of apoptotic cells and increased inflammation [76]. After placing Ldlr^{-/-}Apobec1^{-/-} mice on normal chow for 10 months, we found that fortilin^{TCTP} deficiency (fortilin^{TCTP+/-} compared with fortilin^{TCTP+/+}) reduced atherosclerosis by 27% [23]. There was no difference in body weight, blood pressure, or lipid profile between fortilin^{TCTP+/+}Ldlr^{-/-}Apobec1^{-/-} and fortilin^{TCTP+/-}Ldlr^{-/-}Apobec1^{-/-} mice. This relatively modest decrease in atherosclerosis in these mice was due to the moderate reduction of tissue fortilin^{TCTP} levels (28–30%) secondary to fortilin^{TCTP} heterozygosity (fortilin^{TCTP+/-}) [23]. Mechanistically, the atherosclerotic lesions of fortilin^{TCTP+/-}Ldlr^{-/-}Apobec1^{-/-} mice contained fewer MΦ and more apoptotic cells than those of fortilin^{TCTP+/+}Ldlr^{-/-}Apobec1^{-/-} mice, as shown by terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) staining and flow cytometry analysis [23]. Intriguingly, there was no difference in the number of VSMCs between the two mouse strains, indicating that constitutional deficiency of fortilin^{TCTP} led specifically to a reduction in MΦs and not VSMCs [23].

p53 is a 393-amino-acid, 53-kDa molecule that serves as a human's most critical defense against tumorigenesis. It eradicates genetically deranged cells by apoptosis through two distinct ways—one *dependent* on and the other *independent* of transcription. In transcription-dependent apoptosis, p53 transcriptionally activates nuclear proapoptotic genes, such as NOXA [77], PUMA [78], and BAX [79]. In transcription-independent apoptosis, p53 translocates to the mitochondria, where it directly activates BAX and induces MOMP, leading to the release of cytochrome c and subsequent activation of caspases 9 and 3 [80]. Mice lacking p53 (p53^{-/-}) are normal at birth but in most cases develop spontaneous neoplasms within 6 months [81]. Mutations in the p53 gene are seen in more than 50% of all human cancers, making them the most frequently observed genetic derangement in human cancer. However, it was not until Guevera's report that we fully understood the protective roles of p53 in the cardiovascular system. In experiments comparing p53^{-/-}ApoE^{-/-} mice

with p53^{+/+}ApoE^{-/-} mice, Guevera and coworkers found that atherosclerosis was more aggressive in p53^{-/-}ApoE^{-/-} mice and that the lack of p53 worsened atherosclerosis [82]. Further studies of p53 and atherosclerosis have shown that MΦ p53 is especially important for protecting arteries against atherosclerosis [83, 84]. In cancer cells, the most common—and most efficient—negative regulatory mechanism of p53 is the mutation of the gene itself and the expression of a mutant and dysfunctional protein [85–87]. Although, p53 is maintained in its normal form in human atherosclerotic tissue [88], it could be made completely powerless by a variety of mechanisms, most notably by the presence of p53 inhibitors.

Fortilin^{TCTP} is a p53 inhibitor. It specifically binds the sequence-specific DNA binding domain of tumor suppressor protein p53 and blocks p53-induced transcriptional activation of BAX [14]. The expression of the BAX gene was more abundant in cells from the atherosclerotic aortae of fortilin^{TCTP+/-} Ldlr^{-/-}Apobec1^{-/-} mice than in those from fortilin^{TCTP+/+} Ldlr^{-/-}Apobec1^{-/-} mice [23]. Further, there was no difference in tissue p53 protein levels between these two groups [23]. These findings, when taken together, suggest that the lack of fortilin^{TCTP} allowed p53 to transcriptionally activate BAX and to induce the loss of MΦs through apoptosis, leading to the amelioration of atherosclerosis [23]. It is likely that hypercholesterolemia and cytokines (such as macrophage colony-stimulating factor (M-CSF)) produced in the pro-atherosclerotic microenvironment induce fortilin^{TCTP} in MΦs in the atherosclerotic intima [23]. Fortilin^{TCTP} induced in MΦs in turn protects MΦs from oxLDL-induced, p53-BAX-mediated apoptosis and allows them to proliferate and facilitate atherosclerosis [23] (Fig. 1, Atherosclerosis).

The role of fortilin^{TCTP} in atherosclerosis has been supported by the work of Cho and coworkers. They generated transgenic mice overexpressing fortilin^{TCTP} on the ApoE^{-/-} hypercholesterolemic genetic background (fortilin^{TCTP-Tg}ApoE^{-/-}) and control mice (fortilin^{TCTP-WT}ApoE^{-/-}), placed them on a high fat diet for 16 weeks, and evaluated the degree and extent of atherosclerosis in these mice [89]. They found that fortilin^{TCTP-Tg}ApoE^{-/-} mice exhibited more extensive atherosclerosis than did fortilin^{TCTP-WT}ApoE^{-/-} mice. Unfortunately, the blood pressure of fortilin^{TCTP-Tg}ApoE^{-/-} mice was significantly higher (~ 20 mmHg) than that of fortilin^{TCTP-WT}ApoE^{-/-} mice [89]. Because systemic hypertension (HTN) drives atherosclerosis [90], it remained unclear whether fortilin^{TCTP} itself or HTN-driven by fortilin^{TCTP} overexpression accelerated atherosclerosis in the experimental system [89].

2.2. Systemic Hypertension

When uncontrolled, HTN can lead to myocardial infarction, stroke, and claudication through the acceleration of atherosclerosis and to aortic aneurysm and dissection, heart failure, and renal insufficiency through its direct effects on the end organs [90]. Na,K-ATPase, a member of the P-type ATPase superfamily, is an integral membrane protein and ion pump that hydrolyzes one molecule of ATP to pump three Na⁺ out of the cell in exchange for two K⁺ entering the cell per pump cycle [91]. Structurally, it is a heterodimeric protein composed of a 100-kDa α-subunit that comprises 10 transmembrane segments and a 55-kDa β unit that is a heavily glycosylated type II membrane protein [92]. Four distinct isoforms have been

reported for both α (isoforms $\alpha 1$, $\alpha 2$, $\alpha 3$, and $\alpha 4$ coded for by ATP1A1, ATP1A2, ATP1A3, and ATP1A4 genes, respectively) and β (isoforms $\beta 1$, $\beta 2$, $\beta 3$, and $\beta 4$ coded for by ATP1B1, ATP1B2, ATP1B3, and ATP1B4 genes, respectively) units [92]. Two distinct human diseases—rapid-onset dystonic Parkinsonism and familial hemiplegic migraine—are attributed to the mutation of the ATP1A2 and ATP1A3 genes, respectively [93]. Dostanic-Larson and coworkers mutated the extracellular domain of the $\alpha 2$ isoform of the ATPase to make the normally ouabain-sensitive isoform resistant to ouabain in mice [94]. The mice, although normotensive at baseline, developed systolic hypertension when challenged by adrenocorticotrophic hormone (ACTH), suggesting that Na,K-ATPase plays a role in the pathogenesis of HTN [94]. Jung and others showed that fortilin^{TCTP} binds to the third cytoplasmic domain of the $\alpha 1$ and $\alpha 2$ isoforms of Na,K-ATPase and inhibits the ATPase activity [95]. The same group also reported that transgenic and constitutional overexpression of fortilin^{TCTP} in mice leads to the spontaneous development of HTN (~20 mmHg higher systolic blood pressure [SBP] compared with the wild-type [WT] control) without salt or ACTH challenge. Because VSMC contractility and resting cytosolic calcium (Ca^{2+}) concentration of VSMC from fortilin^{TCTP-Tg} mice were greater than those of VSMC from fortilin^{TCTP-WT} mice, it was speculated that HTN was caused by increased contractility and decreased relaxation of VSMC due to the inhibition by fortilin^{TCTP} of vascular Na,K-ATPase activity and subsequent influx of Ca^{2+} into the cytosol [96]. Because there was no difference in SBP between fortilin^{TCTP+/-} (fortilin^{TCTP} heterozygous deficiency) and fortilin^{TCTP+/+} (WT) mice in our study [23], however, further investigation is needed to clarify the precise role of fortilin^{TCTP} in HTN.

2.3. Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) is a lethal disease characterized by dysregulated growth and apoptosis resistance of pulmonary vascular ECs [97]. Hereditary PAH (HPAH) is often caused by loss-of-function mutations in the bone morphogenetic protein receptor type 2 gene (BMPR2), which is a gene that mediates survival signaling in ECs. Reduced BMPR2 activity likely increases EC apoptosis in response to various environmental triggers [98]. EC apoptosis is an initiating event in experimental PAH that leads either to degeneration of pre-capillary arterioles or the selection of hyperproliferative, apoptosis-resistant ECs that may contribute to occlusive intimal and complex plexiform lesions [97, 98]. It follows that patients with HPAH exhibit increased endothelial apoptosis and subsequent predominance of apoptosis-resistant proliferative ECs [97, 98].

Lavoie and coworkers derived ECs from the blood (blood-outgrowth ECs, or BOECs) of HPAH patients with known BMPR2 mutations and healthy volunteers, extracted proteins from the cells, and subjected them to two-dimensional polyacrylamide gel electrophoresis and liquid chromatography–tandem mass spectrometry analysis (LC-MS/MS) [97]. Eleven proteins were found significantly upregulated and 11 proteins significantly downregulated in BOECs of the HPAH patients compared with those of the healthy volunteers. Fortilin^{TCTP} was one of the 11 proteins that were significantly upregulated in the HPAH patients [97]. Consistently, fortilin^{TCTP} expression was greater in explanted lungs of patients with HPAH and idiopathic PAH than in those of control donor lungs [97]. Further, the lungs from rats with the tyrosine-kinase inhibitor semaxanib (SU5416)-induced PAH exhibited increased

fortilin^{TCTP} expression [97]. However, it was not entirely clear from the study whether fortilin^{TCTP} overexpression was specific to pulmonary ECs or more generalized in cells in the arterial adventitia and their adjacent tissue [97]. Mechanistically, BMPR2 silencing in normal BOECs led to increased fortilin^{TCTP} expression in these cells [97]. Because the lack of BMPR2 led to both overexpression of the anti-apoptotic protein fortilin^{TCTP} and development of PAH phenotypes that are thought to be initiated by apoptosis of ECs, further investigation is needed to elucidate the exact role of fortilin^{TCTP} in the pathogenesis of PAH (Fig. 1, Pulmonary Artery Hypertension).

2.4. Malignant Neoplasms

Although numerous reports show that fortilin^{TCTP} is overexpressed in cancer cell lines, only about dozen studies have evaluated the role of fortilin^{TCTP} in actual human cancer tissue. Here we review the reports that used multiple tissue samples from human cancers with appropriate statistical analyses. The data from these reports overall show that fortilin^{TCTP} is overexpressed in malignant neoplasms and that the higher expression of the molecule is associated with poorer clinical outcomes (Fig. 1, Cancer).

2.4.1. Breast Cancer—Deng and coworkers obtained breast cancer and adjacent normal breast tissues from 12 patients with infiltrating ductal carcinoma, subjected the total tissue lysates from the samples to two-dimensional polyacrylamide gel electrophoresis and matrix-assisted laser desorption/ionization tandem time-of-flight mass spectrometry (MALDI-TOF/TOF-MS), and found that 15 distinct proteins were differentially expressed in 11 of the 12 samples. Among the 15 proteins, 6 were upregulated at least 4-fold. Fortilin^{TCTP} was one of the six proteins, suggesting that it plays an important role in breast cancer pathogenesis [99]. Based on analysis of immunohistochemistry staining of tissue samples from 508 breast cancer patients who were enrolled in a single-center breast cancer surgical trial with 5-year clinical follow up [100], Amson and coworkers divided the breast tumors into two groups: (a) fortilin^{TCTP}-low tumors, in which fortilin^{TCTP} was expressed in < 1% of the parenchymal cells (474 samples) and (b) fortilin^{TCTP}-high tumors, in which fortilin^{TCTP} was expressed in > 1% of the cells (34 samples). High fortilin^{TCTP} status was associated with a poor degree of differentiation, higher proliferative activity, and low negative estrogen receptor expression. In addition, high fortilin^{TCTP} status was associated with a significantly lower 5-year disease-free survival rate, even after adjustments were made for the major clinical and pathological parameters using a multivariate proportional-hazard model [27].

2.4.2. Gastric Cancer—*Helicobacter pylori* (*H. Pylori*) infection is the most important risk factor for peptic ulcer disease, gastric intestinal metaplasia (IM) and cancer [101]. Li and co-workers immunostained tissue samples from patients with gastritis and gastric cancer to examine the expression levels of fortilin^{TCTP} [102]. The expression of fortilin^{TCTP} was negligible in gastritis mucosa but was drastically upregulated in gastric IM and cancer tissues. Fortilin^{TCTP} expression in these lesions was greater in the presence of *H. Pylori* infection than in its absence. Further, when *H. Pylori* infection was present, fortilin^{TCTP} expression was greater with the SlyD-positive *H. Pylori* strain than with the SlyD-negative strain [102]. SlyD is a 196-amino-acid multi-functional bacterial protein that functions as a propyl cis/trans isomerase, nickel-binding protein, and molecular chaperone [103]. The same

investigators showed that recombinant *H. Pylori* SlyD (HpSlyD) induced CDX2 in a fortilin^{TCTP}-dependent fashion in gastric cell lines. Although it is not expressed in the normal stomach, CDX2 has been shown to be highly expressed in the gastric IM [104] and cancer [105]. Forced overexpression of CDX2 in the stomach leads to extensive IM, with subsequent progression to gastric cancer [106]. These data, when taken together, indicate that fortilin^{TCTP} plays a facilitative role in *H. Pylori*-induced gastric carcinogenesis by allowing HpSlyD to induce CDX2, an oncoprotein to the gastric mucosa.

2.4.3. Colorectal Cancer—Bommer and coworkers immunostained surgical samples of colorectal adenomas, adenocarcinomas, and metastatic adenocarcinomas in lymph nodes for fortilin^{TCTP}. Normal colon tissue adjacent to malignant tissue was identified microscopically and used as the control. They calculated the relative staining scores by multiplying the staining intensity (possible scores = 0 [no staining], 1 [weak staining], and 2 [strong staining]) by the numbers of cell stained (possible scores = 0 [0–5% of cells stained], 1 [5–75%], and 2 [> 75%]). Possible relative staining scores were 0, 1, 2, or 4. They found that the relative staining scores of adenomas (the score = ~2.3), adenocarcinomas (~3.0), and metastatic adenocarcinomas (~3.0) were significantly higher than those of normal tissue (~1) [107]. Xiao and coworkers immunostained 134 paired colorectal cancer and adjacent normal tissue samples for fortilin^{TCTP} and found that it was significantly overexpressed in colorectal cancer tissue. They also found that high fortilin^{TCTP} expression was significantly correlated with poor metastasis-free survival in 90 patients with colorectal cancer [108].

2.4.4. Hepatocellular Carcinoma (HCC)—Chan and coworkers performed quantitative reverse transcription polymerase chain reaction (RT-qPCR) on both tumor and adjacent non-tumor tissues of 118 HCC patients and found that fortilin^{TCTP} expression was significantly higher in HCC tissues than in adjacent non-tumor tissues and that fortilin^{TCTP} overexpression was significantly associated with shorter overall survival of patients after hepatectomy [109].

2.4.5. Lung Cancer—Kim and coworkers performed Western blot analyses using anti-fortilin^{TCTP} antibody on matched normal and tumor tissues of 11 lung cancer patients and found that fortilin^{TCTP} expression was greater in lung cancer tissue than in normal lung tissue. The same group of investigators also evaluated plasma levels of fortilin^{TCTP} in 23 lung cancer patients and 17 healthy donors and found that plasma fortilin^{TCTP} levels were significantly higher in lung cancer patients than in healthy donors [110].

2.4.6. Oral Squamous Cell Carcinoma (OSCC)—Lo and coworkers took primary OSCC and adjacent normal surrounding mucosal samples from 12 patients, extracted total proteins from the samples, and subjected them to isobaric tags for relative and absolute quantification (iTRAQ)-based quantitative proteomic analysis. Fortilin^{TCTP} was one of 13 proteins that was upregulated in cancer tissues, which was validated by both RT-qPCR and Western blot analyses [111].

2.4.7. Ovarian Cancer—Chen and coworkers immunostained 119 formalin-fixed, paraffin-embedded epithelial ovarian cancer (EOC) tissues and found that fortilin^{TCTP}

expression was significantly and positively correlated with the International Federation of Gynecology and Obstetrics (FIGO) histological grade and shorter survival [112].

2.4.8. Prostate Cancer—Baylot and coworkers immunostained 112 prostate cancer tissues using tissue microarrays and found that fortilin^{TCTP} was absent or weakly expressed in normal prostate cells, moderately expressed in 18.5% of treatment-naïve prostate cancer cells, and strongly expressed in 75% of castration-resistant prostate cancer cells [113]. Kaarbø and coworkers immunostained fortilin^{TCTP} tissue microarrays of prostate cancer from 357 radical prostatectomy samples and 35 normal prostate samples and found that fortilin^{TCTP} was expressed primarily in prostate epithelial cells and that its expression was significantly increased in cancer tissue compared with normal tissue [114].

2.4.9. Malignancies of Central and Peripheral Nervous Systems—Human glioma is the most common malignancy in the central nervous system for both children and young adults [115]. Miao and coworkers showed that fortilin^{TCTP} expression was significantly higher in human glioma tissues compared with normal brain tissues [116]. Fortilin^{TCTP} expression also was positively correlated with the grade of glioma, where its expression levels were greater in high-grade glioma tissues compared to low-grade glioma samples [116]. Similarly, Gu and coworkers studied fortilin^{TCTP} expression in stage I to V human glioma tissues and in normal brain tissues and found that both fortilin^{TCTP} protein and mRNA levels were significantly upregulated in high-grade gliomas compared to low-grade gliomas [30]. In the study, the higher expression of fortilin^{TCTP} in the tumors was significantly correlated with poorer overall survival rate and with lower post-therapy survival rate following radiotherapy and temozolomide therapies in the patients [30]. Mechanistically, fortilin^{TCTP} potentially promoted glioma cell proliferation and tumor growth by interacting with transcriptional factor 4 (TCF4) and activating the wingless-related integration site (Wnt) signaling pathway and by increasing the expression of cell cycle proteins [19, 30]. Fortilin^{TCTP} also was reported to enhance migration and invasion of glioma cells and astrocytes by increasing matrix metalloproteinase 2 (MMP2) and MMP9 activities and inducing cytoskeletal reorganization, respectively [19, 117].

Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder caused by germ line mutations of the NF1 tumor suppressor gene that encodes neurofibromin. It manifests itself in the development of benign peripheral nerve sheath tumors (neurofibromas), which tend to become malignant [118]. Kobayashi and coworkers found that fortilin^{TCTP} was upregulated in the rat pheochromocytoma cell PC12 and in Schwann cells that were neurofibromin deficient. Growth factor-induced upregulation of fortilin^{TCTP} in neurofibromin-deficient cells was due to (a) the prevention of proteasome-mediated fortilin^{TCTP} degradation and (b) the promotion of fortilin^{TCTP} translation, both of which were positively regulated by the MAPK/PI3K-AKT-mTOR pathway. These data suggest that fortilin^{TCTP} upregulation in neurofibromin-deficient cells protects them against appropriate apoptosis and leads to the development of neurofibromas and other NF1 phenotypes [119].

Yarm showed that polo-like kinase 1 (PLK1) physically interacted with fortilin^{TCTP} and phosphorylated it at the 46th and 64th serine residues (⁴⁶S and ⁶⁴S) and that phosphorylation of these serines in fortilin^{TCTP} by PLK1 was required for the completion of mitosis. Ramani

and coworkers immunostained malignant neuroblastic tumor sections from 88 consecutive patients with anti-phosphorylated (^{46}S) fortilin^{TCTP} (p-fortilin^{TCTP}) antibodies and found that the high expression levels of p-fortilin^{TCTP} were associated with lower cumulative survival of the patients [120], although it is not yet clear how p-fortilin^{TCTP} worsens the prognosis of patients with the tumors.

2.5. Malaria

Malaria is a life-threatening, chronic disease caused by *Plasmodium* parasites that are transmitted to humans through the bites of infected female anopheline mosquitoes. The estimated 515 million cases of human malaria each year are mostly caused by four species: *Plasmodium falciparum*, *P. vivax*, *P. ovale*, and *P. malariae* [121]. *P. falciparum* malaria is the most deadly form of malaria; it is associated not only with fever and anemia but also with neurological problems such as coma and learning difficulties [121]. *P. falciparum* fortilin^{TCTP} (Pf-fortilin^{TCTP}) has been shown to be ubiquitously present—in the cytoplasm, food vacuole, and limiting membranes of the parasite [41]—and it is 33% identical and 54% similar to human fortilin^{TCTP} [10]. MacDonald and others reported that Pf-fortilin^{TCTP} was detectable in the plasma of patients infected with *P. falciparum* at $1.41 \pm 1.44 \mu\text{g/mL}$ as quantified by Western blot analyses (the detection limit of malaria fortilin^{TCTP} = $0.05 \mu\text{g/mL}$), whereas it was absent in uninfected subjects [10, 122]. In the cellular system, recombinant Pf-fortilin^{TCTP} was able to cause primary human basophils to secrete histamine in the presence of IgE, although with half-maximal concentration (EC_{50}) of $100 \mu\text{g/mL}$, which is 10 times higher than the EC_{50} of human fortilin^{TCTP} [10]. In addition, recombinant Pf-fortilin^{TCTP} caused primary human eosinophils to secrete interleukin 8 (IL8), but again less potently than did recombinant human fortilin^{TCTP} [10]. Although the plasma concentration of human fortilin^{TCTP} was not reported in the study [10], these data suggest that Pf-fortilin^{TCTP} circulating in the plasma of malaria-infected patients contributes to the development of inflammatory phenotypes seen in the patients with malaria.

Artemisinin-based combination therapies are strongly recommended and highly effective treatments for uncomplicated *P. falciparum* malaria [123]. Artemisinin and its analogues—artemether, artesunate, and dihydroartemisinin (DHA)—are sesquiterpene lactones [124] whose exact molecular target has been extensively sought. It has been reported that artemisinins specifically and selectively inhibit Pf-ATP6, the sarco/endoplasmic reticulum Ca^{2+} -ATPase [125], and Pf-PI3K, the phosphatidylinositol-3-kinase [126], of *P. falciparum*. Bhisutthibhan and others reported that DHA, but not its inactive congener deoxydihydroartemisinin, covalently binds Pf-fortilin^{TCTP} in the presence of hemin, suggesting that Pf-fortilin^{TCTP} is another molecular target of artemisinins [127, 128], as also supported by Eichhorn and coworkers [129]. To test whether DHA also binds and inhibits human fortilin^{TCTP}, we subjected human fortilin^{TCTP} fused to glutathione S-transferase (GST) to surface plasmon resonance binding assays. We found that DHA specifically bound to GST-human fortilin^{TCTP}, but not to GST alone, at the dissociation constant of $38 \mu\text{M}$ and even in the absence of hemin. In osteosarcoma U2OS cells, the binding of DHA to fortilin^{TCTP} elicited the ubiquitination and proteasome-dependent degradation of fortilin^{TCTP} [56]. Because fortilin^{TCTP} functions anti-apoptotically across species [1, 18, 32,

33, 44, 45, 49, 54, 130], it is tempting to speculate that DHA and other artemisinins bind and degrade Pf-fortilin^{TCTP}, leading to the apoptotic death of the parasites.

Rodent malaria parasites that have become resistant to artemisinin [131, 132] are useful tools for investigating the mechanism of artemisinin resistance. By treating CD1 mice infected with the rodent malaria parasite *P. chabaudi* with an increasing dose of artemisinin, Afonso and coworkers cloned the artemisinin-resistant strains of *P. chabaudi*. They determined the nucleotide sequences and copy numbers of *mdr1*, *cg10*, *fortilin*^{TCTP}, and *atp6*—the genes thought to be involved in the resistance—from both artemisinin-sensitive and -resistant strains and found that none of these genes had either mutations or change in expression levels [133]. Mok and others analyzed the in vivo transcriptomes of 1043 *P. falciparum* isolates from patients with acute malaria and found that the artemisinin-resistant malaria parasites expressed higher levels of molecules of the unfolded protein response pathway [134]. Fortilin^{TCTP} was not one of the genes whose expression levels were significantly associated with artemisinin resistance [134]. On the other hand, Arie and coworkers compared the exomes of the artemisinin-resistant F32-ART5 parasite line with those of the artemisinin-sensitive control line F32-TEM. They identified eight mutations in seven genes in the F32-ART5 line, one of which was the mutation of the 580th cysteine to tyrosine (C580Y) in the Kelch13 protein. Fortilin^{TCTP} was not one of the seven genes mutated in the F32-ART5 line [135]. Thus, it is unlikely that fortilin^{TCTP} plays a role in the development of malaria resistance to artemisinins through either change in expression levels or mutations.

Taylor and others produced recombinant fortilin^{TCTP} proteins from *P. falciparum* (Pf-fortilin^{TCTP}) and murine malaria parasites *P. yoelii* (Py-fortilin^{TCTP}) and *P. berghei* (Pb-fortilin^{TCTP}), immunized mice three times with these fortilin^{TCTP}s, and challenged them with *P. yoelii*, *P. berghei*, and the other murine malaria parasite *P. chabaudi* [136]. Upon immunization, these mice mounted a significant titer of antibodies against the respective fortilin^{TCTP}s. Although immunization with Pf-fortilin^{TCTP} and Py-fortilin^{TCTP} protected the mice against parasitemia from *P. yoelii* and *P. chabaudi* infection, respectively, the protection was modest and confined to the early phase of infection [136]. Intriguingly, immunization by Pb-fortilin^{TCTP} did not protect mice against *P. berghei* parasitemia [136]. There has been no study using neutralizing antibodies against malaria fortilin^{TCTP}s to determine if administration of such antibodies reduces parasitemia. Further investigation is needed to define the effectiveness of vaccination with malaria fortilin^{TCTP}s for the prevention and treatment of human malaria (Fig. 1, Malaria).

2.6. Liver Disease

Excessive alcohol consumption is the third leading preventable cause of death in the United States. Among various causes of alcohol-related death, alcoholic liver disease represents the most significant cause of mortality, to which 44% of all deaths from liver disease are attributed. Affecting predominantly younger people, approximately 30 years of life are lost per alcohol-related death, which translates to about 2.3 million years of potential life lost per year [137].

Fortilin^{TCTP} physically interacts with the antioxidant enzyme peroxiredoxin-1 (PRX1), a 199-amino-acid polypeptide and a member of the peroxiredoxin family (PRXs1–6) [12]. In our study, fortilin^{TCTP} protected PRX1 from proteasome-mediated degradation and kept it enzymatically active by blocking its deactivating phosphorylation by mammalian sterile twenty 1 (Mst1), a serine/threonine kinase [12]. PRX1 is the most active PRX in eliminating reactive oxygen species (ROS) from the livers of alcohol-treated mice, and it protects the liver against alcohol-induced oxidative injury [138]. To test whether overexpression of fortilin^{TCTP} in the liver protects the organ against alcohol-induced oxidative-stress-mediated injury, we generated a strain of transgenic mice that overexpress fortilin^{TCTP} tissue-specifically in the liver (fortilin^{TCTP-Liver-Tg}) and its WT control (fortilin^{TCTP-Liver-WT}). The liver of fortilin^{TCTP-Liver-Tg} mice expressed 35.5-fold and 2.4-fold more mRNA and protein than fortilin^{TCTP-Liver-WT} mice, respectively. We administered 10 g/kg body weight of alcohol over 36 hours to induce acute alcohol-induced liver injury [12]. The levels of alanine aminotransferase, the indicator of liver function, of fortilin^{TCTP-Liver-WT} mice were 4.3-fold higher than those of fortilin^{TCTP-Liver-Tg} mice. The levels of malondialdehyde and 4-hydroxynonenal, indicators of lipid peroxidation, were significantly greater in the livers of fortilin^{TCTP-Liver-WT} mice than in the livers of fortilin^{TCTP-Liver-Tg} mice [12]. Hepatocytes of fortilin^{TCTP-Liver-WT} mice exhibited significantly more apoptosis than those of fortilin^{TCTP-Liver-Tg} mice as examined by TUNEL and fragmented cytokeratin-18 staining [12]. Both PRX1 protein level and activity were higher in the livers of fortilin^{TCTP-Liver-Tg} mice than in those of fortilin^{TCTP-Liver-WT} mice in the presence of the alcohol challenge. Furthermore, PRX1 from fortilin^{TCTP-Liver-WT} mice was more extensively phosphorylated at threonine residues than that from fortilin^{TCTP-Liver-Tg} mice [12]. Taken together, these data suggest that fortilin^{TCTP} protects against alcohol-induced ROS-mediated liver damage by enhancing PRX1 activity, with a decrease in the deactivating phosphorylation of PRX1, and by increasing PRX1 protein level by inhibiting ubiquitination and proteasome-mediated degradation of PRX1. These data suggest that fortilin^{TCTP} plays an important role in the prevention of alcohol-induced liver diseases (Fig. 1, Liver Diseases).

As we recently reported [139], fortilin^{TCTP} interacts with phosphorylated and activated inositol-requiring enzyme 1 α (IRE1 α) and inhibits both kinase and endoribonuclease (RNase) activities of the stress sensor, protecting cells against apoptotic cell death [139]. Because it produces and secretes a massive amount of proteins to the circulation, the liver is particularly vulnerable to endoplasmic reticulum (ER) stress. To test whether fortilin protects the liver against ER-stress-induced damage, we generated a mouse strain that lacked fortilin in the liver by crossing transgenic mice overexpressing the albumin-promoter-drive Cre recombinase (alb-Cre^{+/−}) with fortilin^{TCTP-flox/flox} mice (fortilin^{TCTP-KO-Liver} mice) [139]. We challenged the mice with EGF-SubA, a highly selective ER stress-inducing agent [140–142]. EGF-SubA is a fusion protein with the epidermal growth factor (EGF) fused to the proteolytic A subunit of a bacterial AB₅ toxin (SubA). Cells internalize EGF-SubA through their EGF receptors. Once in the cytosol, EGF-SubA is retrogradely transported via the Golgi system to the ER lumen, where it cleaves and destroys GFP78 (also known as BiP), an ER resident master stress regulator protein, initiates the unfolded protein response (UPR), and activates all three key ER transmembrane stress sensors—IRE1 α , PERK, and ATF6 [140–142]. We found that EGF-SubA challenge caused fortilin^{TCTP-KO-liver} mice to

develop fulminant liver damage and died within 48 hours while fortilin^{TCTP-WT-liver} control mice showed only minimal liver damage. The livers of EGF-SubA-challenged fortilin^{TCTP-KO-liver} mice, but not those of fortilin^{TCTP-WT-liver} mice, exhibited both (a) the activation of IRE1 α and its downstream (JNK and XBP1) pathways and (b) the apoptotic death of hepatocytes. Because KIRA6, an imidazopyrazine-based small-molecule IRE1 α inhibitor, completely reversed the pathological changes seen in the livers of EGF-SubA-challenged fortilin^{TCTP-KO-liver} mice [139], it was likely that fortilin protected the EGF-SubA-challenged liver through its specific inhibition of the IRE1 α pathway, not through its inhibition of other apoptotic pathways such as the ones involving p53 [24, 27], MCL1 [21, 26], BCL-XL [25], MOMP [2], or Ca²⁺ [17]. It is likely that fortilin^{TCTP} protects the liver against ER-stress-inducing diseases, such as viral hepatitis where hepatitis viruses rely on the host's hepatic transcription machinery to produce their structural and non-structural proteins essential for replication.

The liver possesses a remarkable capacity for regeneration. Upon partial hepatectomy, terminally differentiated hepatocytes in the remaining liver enter the cell cycle and regenerate liver mass within weeks [143], although the exact mechanism and genes involved in the process are incompletely understood. Hao and coworkers found that fortilin^{TCTP} is robustly expressed in the liver after partial hepatectomy [31]. When treated with neutralizing anti-fortilin^{TCTP} antibody, the livers of partially hepatectomized rats exhibited a lower ratio of bromodeoxyuridine-positive cells and incomplete regeneration compared with control IgG treatment [31]. Anti-fortilin^{TCTP} antibody treatment also decreased the expression levels of cell cycle promoting proteins cyclin-dependent kinase 2 (Cdk2) and cyclin E2 as well as tumor necrosis factor alpha (TNF α), interleukin 6 (IL-6), and signal transducer and activator of transcription 3 (STAT3) [31], which have been shown to prime hepatocytes to regenerate [144]. Although the intravenous administration of recombinant rat fortilin^{TCTP} failed to increase the liver-body weight ratio of partially hepatectomized rats in the study [31], it is possible that recombinant fortilin^{TCTP} needed to be delivered to the direct vicinity of regenerating hepatocytes to be effective [31]. Further investigation may more definitively show the facilitative role of fortilin^{TCTP} in liver regeneration.

2.7. Biomarkers of Total Body Apoptosis

Billions of cells undergo apoptosis each day in the average normal adult [145]. Serum biomarkers of apoptosis—molecules that can be readily and objectively measured as indicators of normally and pathologically occurring apoptosis at tissue and organ levels—would allow clinicians to monitor the status of apoptosis associated with the diseases they treat, such as apoptosis-induced skeletal muscle atrophy resulting from cancer (cachexia) and aging (sarcopenia). Cancer cells undergo apoptosis at a higher rate than do normal cells and massively apoptose in response to radiation therapy and chemotherapy. Serum biomarkers of apoptosis could allow clinicians to screen patients for certain cancers and to monitor the response of patients with cancer to anti-cancer chemo- or radiation therapy [4].

To test whether fortilin^{TCTP} exists in the circulating blood, we devised a fortilin^{TCTP} enzyme-linked immunosorbent assay (ELISA) assay system and found that fortilin^{TCTP} circulates in the blood of both mice and humans at the concentration of 47.10 ± 11.66 ng/mL

and 75.57 ± 45.79 ng/mL, respectively [4]. Fortilin^{TCTP}, an intracellular anti-apoptotic molecule, is also released into the extracellular space via secretory exosomes [3]. To test whether serum fortilin^{TCTP} levels reflect the degree of apoptosis occurring at the tissue level, we subjected to fortilin^{TCTP} ELISA the pre- and post-treatment sera of patients with solid cancer who were undergoing anti-cancer chemo- or radiation therapies known to cause apoptosis in the cancerous cells. We found that anti-cancer therapy caused the mean serum fortilin^{TCTP} levels to increase 2.4-fold without increasing the levels of the necrosis marker lactate dehydrogenase (LDH) for most cases [4]. Serum fortilin^{TCTP} levels were also found to be a more sensitive indicator of in vivo apoptosis than serum levels of the conventional apoptosis markers such as cytochrome c, nucleosomal DNA, and fragmented cytokeratin-18 [4]. Next, we intraperitoneally challenged C57BL/6J mice with Armenian hamster anti-Fas-antigen (Jo2) antibody, induced Fas-mediated hepatocyte apoptosis [146], and measured the serum levels of fortilin^{TCTP} before and after the antibody challenge. Serum fortilin^{TCTP} levels increased 2.63-fold following Jo2-antibody challenge and hepatocyte apoptosis [4]. These data suggest that serum fortilin^{TCTP} levels can be used as a surrogate marker of in vivo apoptosis.

2.8. Diabetes Mellitus (DM)

DM, a syndrome characterized by signs and symptoms of chronic hyperglycemia, is one of the largest epidemics the world has faced, affecting over 400 million people worldwide [147]. Patients with diabetes do not have a pancreatic β -cell mass large enough to produce the amount of insulin needed to maintain normal blood glucose levels. Diraison and coworkers compared the protein expression patterns of MIN6 pancreatic β -cells treated with 3 mM (54 mg/dL) of glucose with those of the same cells treated with 25 mM (450 mg/dL) of glucose using 2D-gel electrophoresis and MALDI-TOF-based analyses. They identified 11 proteins whose expression was upregulated by glucose, one of which was fortilin^{TCTP} [15]. Glucose stimulation increased the expression levels of fortilin^{TCTP} by 1.8- to 2.5-fold, dephosphorylated the serine and tyrosine residues of the molecule, and translocated it from the cytosol to the nucleus [15]. Consistent with the previously reported anti-apoptotic function of fortilin^{TCTP}, small interfering RNA (siRNA)-based fortilin^{TCTP} knockdown and plasmid-based fortilin^{TCTP} overexpression in MIN6 cells led to the increase and reduction of apoptosis in the cells, respectively [15]. It remains unknown, however, whether glucose-induced fortilin^{TCTP} expression is specific to pancreatic β -cells and does not occur in other tissues and cells. Because serum stimulation has been shown to increase fortilin^{TCTP} expression [26, 148], glucose is just one of the inducers of fortilin^{TCTP}. Nevertheless, it is likely that fortilin^{TCTP} protects pancreatic β -cells against apoptosis precipitated by hyperglycemic stress [15].

Diabetic nephropathy (DN) is a major chronic complication that develops in 20–40% of patients with DM and represents the most common cause of end-stage renal disease in the US [149]. Damage to the glomerular filtration barrier—consisting of glomerular endothelial cells, glomerular basement membrane, and podocytes—leads to the leakage of plasma proteins into the urine (or proteinuria) and other functional and morphological changes typically seen in DN. Podocytes are the visceral epithelial cells and play a key role in the pathogenesis of DN. The density of the cells decreases and the morphology changes

(hypertrophy and retraction of the foot processes (or effacement) of the cells) as clinical DN progresses [149]. Kim and coworkers reported that fortilin^{TCTP} expression was greater in the glomeruli of DM mice than in those of control mice. They then generated lentiviral vectors containing both the expression cassette of the enhanced green fluorescence protein (EGFP) and either control or the short-hairpin (sh) silencing sequence of fortilin^{TCTP} (lentivirus-EGFP-control and lentivirus-EGFP-sh-fortilin^{TCTP}, respectively), injected them through the tail veins of control and DM mice, and evaluated the functional and morphological changes of their kidneys. At baseline, there were fewer podocytes in the glomeruli of DM mice than in those of control mice. In addition, the podocytes in DM glomeruli were hypertrophied when compared to those in control glomeruli. Treatment with lentivirus-EGFP-sh-fortilin^{TCTP}, but not lentivirus-EGFP-control, ameliorated hypertrophy and protected against DM-induced podocyte apoptosis, leading to the improvement of proteinuria in these mice. Mechanistically, silencing of fortilin^{TCTP} inhibited the phosphorylation and activation of eukaryotic translation initiation factor 4E binding protein 1 (EIF4EBP1) and ribosomal protein S6 kinase β -1 (P70S6K), which are effector molecules of the mechanistic target of the rapamycin (mTOR) pathway that is involved in cell hypertrophy. Silencing of fortilin^{TCTP} also decreased the expression of cyclin-dependent kinase inhibitor proteins p21 and p27 in the glomeruli of the DM mice, potentially leading to podocyte proliferation to compensate for DM-induced podocyte apoptosis and loss. Kim's data suggest that fortilin^{TCTP} represents a viable molecular target for the prevention and treatment of DN [150]. The apparent facilitative role of fortilin^{TCTP} in podocyte apoptosis observed in the study calls for further investigation, as fortilin^{TCTP} normally protects cells against apoptosis.

Tsai and colleagues observed that fortilin^{TCTP} was robustly expressed in pancreatic β -cells during the embryonic and postnatal periods and that its expression rapidly declined thereafter. They then generated β -cell-specific fortilin^{TCTP} knockout and control mice (fortilin^{TCTP}-KO- β -cell and fortilin^{TCTP}-WT- β -cell mice, respectively) [36]. Although fortilin^{TCTP}-KO- β -cell mice were grossly normal and had the same weight and life span as fortilin^{TCTP}-WT- β -cell mice, fortilin^{TCTP}-KO- β -cell mice showed a lower β -cell density in the pancreas and exhibited lower resting and glucose-stimulated insulin secretion rates as well as higher post-prandial glucose levels than did fortilin^{TCTP}-WT- β -cell mice. These results suggested that the smaller β -cell mass seen at the time of birth in fortilin^{TCTP}-KO- β -cell mice contributed to the insufficient insulin production and diabetic phenotype in adulthood. Importantly, they also found that β -cells did not proliferate or expand in response to a high fat diet in fortilin^{TCTP}-KO- β -cell mice, unlike the case with fortilin^{TCTP}-WT- β -cell mice, suggesting that fortilin^{TCTP} is critical for β -cells to proliferate and adapt to meet the body's increased need for insulin in adulthood. Mechanistically, fortilin^{TCTP}-deficient β -cells exhibited impaired activation of the mTOR pathway, as evidenced by decreased phosphorylated P70S6K, upregulation of p53, and downregulation of cell cycle promoting genes including cyclin D2 and cyclin-dependent kinases. This finding is consistent with the above report from Kim and coworkers [150]. Tsai's work is the first to demonstrate the facilitative role of fortilin^{TCTP} in the development and adaptive response of pancreatic β -cells in whole animals [36] (Fig. 1, Diabetes).

2.9. Developmental Abnormalities

Fortilin^{TCTP} plays a key role in development. We reported that fortilin^{TCTP}^{-/-} mice generated by targeted disruption of the gene were embryonically lethal and could not survive beyond 3.5 post-coital days (dpc), although fortilin^{TCTP}^{+/-} mice were healthy and fertile with a normal life span [20]. Blastocysts from fortilin^{TCTP}^{-/-} embryos failed to outgrow or prematurely disintegrated and were unable to produce either inner cell mass or trophoblasts [20]. Mouse embryonic fibroblasts (MEFs) established from fortilin^{TCTP}^{+/-} embryos were more sensitive to noxious stimuli than those from WT embryos [20]. The overexpression of *Xenopus* fortilin^{TCTP} (X-fortilin^{TCTP}) in 4-cell stage *Xenopus* embryos led to secondary axis formation without inducing *Goosecoid* and *Xnr3*, the axis-forming genes, while silencing of it inhibited proper axis formation in the embryos [20]. An animal cap assay showed that X-fortilin^{TCTP} prevented the other axis-forming gene BMP4 from inducing its target genes *Vent1*, *Vent2*, and *Msx1*, suggesting that X-fortilin^{TCTP} is an inhibitor of the BMP4 pathway [20]. In the absence of fortilin^{TCTP}, BMP4 induced *Msx2*—a proapoptotic protein and paralog of *Msx1*—and caused MEFs to apoptose [20]. These data suggest that the lack of fortilin^{TCTP} in mouse embryos led to overactivation of the BMP4 pathway, induction of the proapoptotic protein *Msx2*, and massive apoptosis of the embryos in the very early phase of development [20].

Chen and coworkers deleted exons 3 and 4 of the fortilin^{TCTP} gene and generated the fortilin^{TCTP} deletion-mutant allele consisting of exons 1, 2, 5, and 6 [13]. Consistent with our findings, their fortilin^{TCTP}^{-/-} mice were embryonically lethal [13]. Their fortilin^{TCTP}^{-/-} embryos exhibited excessive apoptosis and defective proliferation, were severely disorganized in structure, and died around 9.5–10.5 dpc [13], whereas our fortilin^{TCTP}^{-/-} embryos died much earlier (~3.5 dpc) [20]. Exons 1, 2, 3, 4, and 5 of the fortilin^{TCTP} gene consist of 28, 74, 191, 106, and 117 nucleotides, respectively, whereas exon 6 consists only of a stop codon (TAA). The deletion of exons 3 and 4 would result in a chimeric protein comprising the 34 amino acids from exons 1 (9 amino acids) and 2 (25 amino acids) and with up to 39 amino acids from exon 5 (depending on how splicing between exons 2 and 5 occurs). Because their anti-fortilin^{TCTP} antibody was raised against the 11th–172nd amino acids of fortilin^{TCTP} [21] and because the chimeric protein may have been very small (with the minimal and maximal sizes of 34 and 73 amino acids, respectively), the antibody may have failed to detect the presence of the chimeric protein. If that is the case, the chimeric protein, being partially functional, could have prevented embryos from undergoing very early apoptotic death as seen in our study [20]. In keeping with this idea, Susini and coworkers deleted exons 3, 4, and 5 of the fortilin^{TCTP} gene and generated the fortilin^{TCTP} deletion-mutant allele consisting of exons 1, 2, and 6 [2], in which the N-terminal 34 amino acids of fortilin^{TCTP} would be expressed. Consistent with our finding and that of Chen, Susini's fortilin^{TCTP}^{-/-} mice were embryonically lethal between 6.5–9.5 dpc, once again exhibiting excessive apoptosis and defective proliferation [2]. Interestingly, zero fortilin^{TCTP} expression in embryos that lack exons 1–5 resulted in very early embryonic lethality around 3.5 dpc [20], whereas the expression of N-terminal 34 amino acids or more allowed the embryos to live until 6.5–9.5 [2] and 9.5–10.5 dpc [21], respectively. This finding suggested that the N-terminal end of fortilin^{TCTP} has an important survival function. Hsu and coworkers reported that the constitutional silencing of *Drosophila* fortilin^{TCTP} resulted in

100% lethality around the third instar larval stage, while reduced fortilin^{TCTP} levels resulted in smaller cell size, cell number, and organ size [34]. They also found that fortilin^{TCTP} directly interacted with Ras homologue enriched in brain (Rheb) and stimulated the guanosine-5'-triphosphate/guanosine-5'-diphosphate (GTP/GDP) exchange on Rheb [34]. These data suggested that fortilin^{TCTP} promotes cell growth and proliferation during development by binding to Rheb and positively regulating its activity [34]. The same group also reported that *Drosophila* 14-3-3 proteins are required to promote the interaction between fortilin^{TCTP} and Rheb, and the loss of 14-3-3-proteins critically impaired organ growth during *Drosophila* development [35]. It is likely that the developmental role of fortilin^{TCTP} is both the prevention of inappropriate apoptosis and the facilitation of cell proliferation and growth through the negative and positive regulations of the apoptosis [2, 20, 21] and mTOR growth pathways [34, 35], respectively (Fig. 1, Developmental Abnormalities).

3. FORTILIN^{TCTP} IN INVERTEBRATE DISEASES

3.1. White Spot Syndrome Virus Infection in Shrimp

Shrimp mount immediate and multiple innate immune responses when pathogens breach their structural barriers [151]. First, the host pathogen recognition receptors (PRPs) on the cell surface recognize the pathogen-associated molecular patterns of the invader and cause the circulating hemolymph and hemocytes to activate humoral and cellular immunity, respectively [42]. White spot syndrome virus (WSSV), a rod-shaped enveloped virus with a double-stranded DNA genome, represents one of the major and serious pathogens in the shrimp industry [51]. Bangrak and coworkers performed a subtraction hybridization of mRNAs from control and WSSV-infected hemocytes from *Panaeus monodon* shrimp [152]. One of the genes that was severely downregulated in WSSV-infected and terminally-ill shrimp was fortilin^{TCTP} (Pm-fortilin^{TCTP}) [43]. Because Pm-fortilin^{TCTP} message levels in WSSV-infected shrimp were drastically elevated in the first 6–12 hours of the viral infection and Pm-fortilin^{TCTP} protects cells against apoptosis [45], it is possible that Pm-fortilin^{TCTP} represents a component of humoral or cellular immunity and is induced in the acute phase of infection to protect hemocytes against apoptosis. Tonganunt and coworkers administered recombinant Pm-fortilin^{TCTP} (rPm-fortilin^{TCTP}) either orally or intramuscularly to WSSV-infected shrimp and found that rPm-fortilin^{TCTP} protected them against viremia and death [52]. In a similar experiment using the white shrimp *Litopenaeus setiferus*, Wu and coworkers found that silencing of fortilin^{TCTP} led to increased viral titers and expression of the viral envelop protein VP28 in the shrimp [53]. Nupan and coworkers infected Sf9 insect cells overexpressing Pm-fortilin^{TCTP} or harboring the empty vector with WSSV and found that Pm-fortilin^{TCTP} protected the Sf9 cells against cell death by inhibiting the expression of key viral proteins such as DNA polymerase, VP15, and VP28 [47]. The same group of scientists reported a 93-amino-acid polypeptide that specifically bound the N-terminal region of Pm-fortilin^{TCTP} (fortilin^{TCTP} binding protein 1 or FBP1) that contained a putative PRP motif [48], although further investigation may be necessary to elucidate how fortilin^{TCTP} collaborates with FBP1 to mitigate WSSV infection [48]. In an experiment using the Indian prawn *Fenneropenaeus indicus*, Rajesh and coworkers reported that both oral and intramuscular administration of the prawn fortilin^{TCTP} protected against WSSV-

induced, ROS-mediated, hemocyte death and improved survival of the WSSV-challenged organism [49]. Taken together, shrimp/prawn fortilin^{TCTP} induced by WSSV infection protects hemocytes against apoptosis, inhibits the expression of viral genes, reduces viremia, and improves survival of the infected shrimp, whereas insufficient expression of fortilin^{TCTP} in response to the viral infection leads to exacerbation of viremia and death. The fact that oral or parenteral administration of fortilin^{TCTP} to WSSV-infected shrimp and prawn improves the prognosis of the infection has an important translational implication, where fortilin^{TCTP} or the bioactive fragments or peptides of fortilin^{TCTP} could be used to protect shrimp and prawn against the lethal viral infection (Fig. 1, Host Defense).

3.2. Bacterial and Viral Infection in Fish, Shellfish, and Worms

Wei and colleagues found that fortilin^{TCTP} from the orange-spotted grouper *Epinephelus coioides* (Ec-fortilin^{TCTP}) protects the fathead minnow fish cell line against cycloheximide-induced apoptosis [130]. Ec-fortilin^{TCTP} was upregulated in the livers of the fish infected with Singapore grouper iridovirus (SGIV). Overexpression of Ec-fortilin^{TCTP} decreased the expression of the major capsid protein and the replication of SGIV in grouper spleen cells infected by the virus. Fortilin^{TCTP} has also been cloned in the salt water clam *Venerupis philippinarum* [153], the sea cucumber *Stichopus monotuberculatus* [50], and the Zhikong scallop *Chlamys farreri* [46], and it was found to be upregulated in the immune cells of the organisms in the early phase of bacterial infection and pathogen challenge. Wang and coworkers constructed a T7 phage display cDNA library from the silkworm (*Bombyx mori*) midgut and screened for proteins that recognized and bound (a) molecules with the pathogen-associated molecular patterns (PAMP), such as lipopolysaccharide (LPS) and chitin or (b) microorganisms pathogenic to the silkworm, such as *Bacillus bombyseptieus* (*Bb*) and *Serratia marcescens* (*Sm*). *Bombyx mori* fortilin^{TCTP} (Bm-fortilin^{TCTP}) was identified as the only protein that bound LPS, chitin, *Bb*, and *Sm*. The oral administration of *Bb* and *Sm* induced the expression of Bm-fortilin^{TCTP} in the midgut of the worm. Bm-Fortilin^{TCTP}-coated *Sm* was phagocytosed by silkworm hemocytes more rapidly than was bovine serum albumin (BSA)-coated *Sm*. The addition of Bm-fortilin^{TCTP} to the culture medium caused the silkworm cell line BmNSWU1 to upregulate the expression of Cecropin A1 and Attacin, which are anti-microbial peptides (AMPs) [154]. The same group of investigators generated transgenic silkworms that tissue-specifically overexpressed siRNA against Bm-fortilin^{TCTP} RNA. The transgenic silkworms expressed 30–43% less Bm-fortilin^{TCTP} in the midgut and were more susceptible to *Sm* and *Staphylococcus aureus* challenge, mounting a smaller amount of Cecropin A1 [155]. These data suggest that Bm-fortilin^{TCTP} protects the worms against bacterial infection through its binding to bacteria and the facilitation of their phagocytic clearance by the hemocytes as well as induction of the AMP (Fig. 1, Host Defense).

4. CONCLUSION

Fortilin^{TCTP} plays an important role in the pathogenesis of human and animal diseases and in developmental abnormalities through its diverse biological activities. Fortilin^{TCTP} facilitates the pathogenesis of atherosclerosis through its inhibition of macrophage apoptosis in the intima of the artery [23]. Fortilin^{TCTP} overexpression leads to systemic hypertension

through its direct binding to and inhibition of Na,K-ATPase [95, 96], while it is not clear how fortilin^{TCTP} contributes to pulmonary arterial hypertension [97]. Fortilin^{TCTP} plays an important role in a number of malignant neoplasms including breast [27, 99, 100], gastric [102], colorectal [107, 108], liver [109], lung [110], oral [111], ovarian [112], and prostate [113, 114] cancers and central and peripheral nervous system tumors including glioma [19, 30, 116], neurofibromatosis [119], and neuroblastomas [120]. It is likely that tumorigenicity of fortilin^{TCTP} is mediated by its ability to protect malignant cells against apoptosis [1, 12–14, 16, 17, 20, 22, 55, 56]. Fortilin^{TCTP} also contributes to the pathogenesis of diabetic nephropathy [150] and is important for the adaptive expansion of pancreatic β -cells in response to obesity and increased insulin requirement [36] and the regeneration of liver after hepatectomy [31]. Fortilin^{TCTP} does this most likely by positively regulating the mTOR signaling pathway [34, 35, 57–59]. The protection by fortilin^{TCTP} of the liver against acute alcohol injury is mediated by its ability to interact with and potentiate the activity of PRX1 [12]. Fortilin^{TCTP} also protects the liver against ER-stress-induced apoptotic injury by binding and inhibiting activated and phosphorylated IRE1 α [139]. In addition, Fortilin^{TCTP} plays a key role in embryo and organ development in vertebrates, as its complete absence results in embryonic lethality due to massive apoptosis [2, 13, 20] and its partial absence results in intrauterine growth retardation [34]. The lack of fortilin^{TCTP} has been shown to decrease cell size, cell number, and organ size in both animals and plants due to the lack of appropriate activation of the mTOR cell growth and proliferation pathway [34, 35, 62, 63]. Further, fortilin^{TCTP} is secreted by cells, circulates in the blood, and serves as a viable surrogate marker for in vivo apoptosis [4]. Finally, in fish [130], shrimp [43, 45, 47–49, 52, 53], and silkworms [154, 155], fortilin^{TCTP} participates in host defense against bacterial and viral pathogens through its ability to (a) recognize, bind, and facilitate degradation of the invaders when secreted into the extracellular space and (b) protect immune cells against pathogen-induced cell death while within the cell. Further research could prove fortilin^{TCTP} to be a viable molecular target for diagnosing and treating various human diseases, including and not limited to atherosclerosis, hypertension, cancer, DM, DN, hepatic injury, and aberrant immunity and host defense (Figure 1).

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Figure 1. The roles of fortilin^{TCTP} in diseases of humans and animals

The anti-apoptotic activities of fortilin^{TCTP} (orange color) contribute to atherosclerosis, pulmonary arterial hypertension, and cancer. Activation of the mTOR pathway by fortilin^{TCTP} (green color) in pancreatic β -cells protects against diabetes. Potentiation of PRX1 and its ROS-scavenging activities by fortilin^{TCTP} (pink color) protects the liver against alcohol-induced damage. Fortilin^{TCTP} also protects the liver against ER-stress-induced damage by binding and inhibiting activated IRE1 α (pink color). Appropriate regulation of both anti-apoptotic and mTOR-activating activities of fortilin^{TCTP} (blue color) is critical for normal growth and development. Extracellular fortilin^{TCTP} (yellow) promotes systemic inflammation in malaria-infected patients but helps invertebrates fight bacterial and viral infection.