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REVIEW

Stanniocalcin-1: A Novel Mediator in Diabetic Kidney Disease and Cardiovascular Disease

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Diabetes mellitus represents a group of metabolic diseases characterized by hyperglycemia from defects in insulin secretion, action, or both. The prevalence of type 2 diabetes mellitus, characterized by insulin resistance, has increased over time in the UK, and is the most prevalent cause of chronic kidney disease (CKD). Cardiovascular complications are a major cause of mortality for these patients.

Stanniocalcin (STC), originally identified in bony fish as a hormone regulating calcium levels, has since been found in mammals, including humans. In fish, STC functions as an antihypercalcemic factor. Mammals possess 2 STC orthologues, STC-1 and STC-2, with STC-1 demonstrating significant sequence and functional conservation across species. Unlike fish, STC-1 is not normally present in the blood of healthy humans. However, it can be detected in certain conditions such as pregnancy, cancer, and CKD. In humans, STC-1 has diverse roles, including modulation of calcium and phosphate homeostasis, and it is implicated in kidney and cardiovascular protection. It has been reported that STC-1 has antioxidant, anti-inflammatory, and antiapoptotic activities, playing a role in renoprotection in diabetic nephropathy.

This review explores the molecular biology of STC-1, its physiological functions, and its emerging role in GKDs, particularly diabetic and cardiovascular diseases. We highlight its potential protective mechanisms against hypercalcemia, its antioxidant and anti-inflammatory properties, and its cardioprotective properties in ischemia-reperfusion.

Further research into STC-1 could provide new insights into therapeutic strategies for managing diseases characterized by calcium imbalance and lead to new treatments for the cardiovascular morbidity associated with diabetic kidney disease.

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Diabetes mellitus represents a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, action, or both.[1] The prevalence of type 2 diabetes mellitus, characterized by insulin resistance, has increased over time in the UK, from 3.14% in 2004 to 5.26% by 2014.[2] Global prevalence of diabetes is projected to continue to increase from 9.3% in 2019 to 10.9% by 2045, driven by aging populations and lifestyle factors.[3]

Diabetes is by far the most prevalent cause of CKD, with a prevalence of 40% in patients with end-stage renal disease.[4] Cardiovascular complications are a major cause of mortality of patients with CKD, and patients with diabetic kidney disease have a particularly high risk of these complications. The additive cardiovascular hazards of diabetes and CKD have been demonstrated in many settings, from the increased additive risk of acute coronary syndrome, arrythmias, congestive heart failure, as well as the risk of complications and mortality associated with these comorbidities.[5]

Among medically treated patients with diabetes undergoing percutaneous coronary intervention, the presence of CKD has been associated with a significantly higher in-hospital and 1-year mortality rate, as well as longer hospital stays and higher rates of neurological, gastrointestinal, and pulmonary complications.[6] Data from the Bypass Angioplasty Revascularization Investigation study among patients with multivessel coronary artery disease undergoing revascularization show an increased risk of death among patients with CKD, independent of and additive to the

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risk associated with diabetes, reaching close to 70% in 7 years in this group.[7] Further understanding of the molecular mechanisms driving the interplay between diabetes, CKD, and cardiovascular disease may open up opportunities for very high impact improvements in morbidity and mortality for patients with diabetic kidney disease.

STC, previously known as both hypocalcin and teleocalcin, is a homodimeric glycoprotein hormone originally isolated from bony (teleost) fish.[8] It was initially identified as a secreted hormone from the corpuscles of Stannius, small endocrine glands located on the ventral surface of the kidneys of fish which lack a parathyroid gland.[9] Surgical removal of the glands in fish resulted in hypercalcemia.[10] The hormone responsible, STC, was isolated and purified from this gland by several groups in the 1980s.[8,11] Thus, in fish, its function was identified as an antihypercalcemic factor.

In mammals, an orthologue was discovered with 61% identity and 73% similarity with various fish STCs, now named STC-1.[12] A few short years later, a second member of the STC family (now named STC-2) was identified in mammals with a much lower sequence similarity and tissue expression profile to the original mammalian STC (now renamed to STC-1) and eel STC.[13]

Humans lack these endocrine glands on the ventral surface of the kidneys (perhaps not wholly surprising given the different embryological development of the kidneys in humans when compared to fish); however, STC-1 has been identified in high concentrations within the adult human kidney, through Western blotting.[14] In humans, unlike in fishes, it does not normally circulate in the blood of normal healthy individuals[15]; however, its serum levels increase to detectable levels in some situations, such as during pregnancy[16] and in cancer.[17]

When human STC-1 is injected into fish it can indeed lower calcium levels[18]; however, injection of recombinant STC-1 into rats did not affect their serum calcium levels. The antihypercalcemic effect that may have been observed was likely masked by the effects of parathyroid hormone (PTH) in these animals.[19] Human STC-1 have been shown to work on isolated intestinal tissue of rats and pigs; decreasing calcium absorption and increasing phosphate absorption 20. This suggests that in the absence of PTH, STC-1 may complement the role of calcitonin and prevent hypercalcemia.

In other organs, STC-1 has been shown to be a pleiotropic hormone, with roles in ovarian physiology, metabolic physiology, and has been upregulated by some cancers. Evidence for the wide-ranging role of this hormone comes from observations in transgenic mice with STC-1 overexpression, which demonstrate growth retardation and leaner muscle mass,[20] coupled with studies that show that the dimer can bind to receptors within the mitochondria.[21]

This review discusses the molecular biology of this evolutionarily preserved hormone, evidence of its role in each of its purported functions in the kidney and cardiovascular system, and a potential emerging role as a mediator between chronic renal disease (and especially so in diabetic kidney disease), where patients often experience hypercalcemia due to secondary hyperparathyroidism, and cardiovascular disease in humans.

The Structure and Molecular Biology of STC

Molecular Structure

As a hormone, STC-1 exists as a homodimeric glycoprotein, with a molecular weight of approximately 54 kDa, found in the genomes of all vertebrates. Human STC-1 consists of monomeric units of 247 amino acids, with an estimated molecular mass of 27 kDa. The monomeric units contain 5 intramolecular disulphide bridges and dimerizes through the C-terminal Cys-202 residue to adopt a dimeric, slightly ellipsoidal shape in solution. It has been characterized as a well-structured protein with 52% alpha helical content.[22]

Human STC-1 shares 76% sequence homology to that of the fish in which it was originally discovered. The first 204 amino acids of human STC-1 share a 92% similarity to that of salmon STC.[12,23] Human STC-1 dimerizes at the same residues as that of fish STC. These dimeric forms are sometimes referred to as "STC50." Other multimeric forms, collectively known as "big STC" have also been described in ovarian and adipocyte and adrenocortical cells, with molecular weights of 84, 112, and 135 kDa,[24] though crystallographic studies could not further substantiate these multimers in the native state of the protein. It has been hypothesized that these multimeric forms may only be possible after posttranslational modifications to the protein.[22] This "big STC" does not appear to be present in the kidney, where STC50 is synthesized and/or are targeted to.

Common posttranslational modifications to the protein include glycosylation; intracellularly it appears to be present in lightly glycosylated forms; however, when secreted it becomes heavily glycosylated and phosphorylated by protein kinase C, from experiments done in fibrosarcoma cells.[25]

Despite some structural similarities, it does not appear that STC-1 is able to form heterodimers with STC-2.[26] STC-2, in contrast to STC-1, only shares 34% identity to human STC-1. Indeed, the lack of spatial conservation of the cysteine residue used for

dimerization and several additional cysteine residues for intramolecular disulphide bonds suggest that STC-2 has a very different tertiary structure from STC-1 or fish STC. However, phylogenetic analysis and comparison of the genomic structure of the STC genes in vertebrates indicated that the STC-1 and STC-2 genes were likely derived from a common ancestor gene. A paralog of STC-2 has subsequently been discovered in fish genomes, again appearing to serve a very different physiological role to STC-1.[27,28]

Expression Profile and Release

STC-1 has been found to be expressed to some degree in a wide range of mammalian tissues, with reports indicating potentially some expression in heart, lungs, liver, adrenal gland, kidney, ovary, prostate, colon, bone and spleen.[29] It has been suggested the low-level expression in many of these tissues is due to a putative paracrine signaling role for STC-1 in many organs. The highest indisputable expression levels for STC-1 mRNA in humans by far are found in the lung, ovary, kidney, prostate, and thyroid.[14] STC2, by contrast appears to predominantly be expressed in the pancreas, again suggesting a very different role for this homolog.[30]

Physiological Functions of STC-1

The physiological role for STC-1 appears on the surface, very different in bony fish compared to mammals. STC exists in fish lacking a parathyroid gland and appears to be responsible for calcium homeostasis, whereas in mammals this role is predominantly taken by the PTH.

Fish STC Acts as an Antihypercalcemic Factor

Fish STC secretion is stimulated by high serum calcium. An increase in serum calcium stimulates both its synthesis and release, sensed by a 7-transmembrane calcium sensing receptor.[31] Evidence for this comes from the ability to stimulate secretion through the use of positive allosteric modulators of the calcium sensing receptor, which increase its sensitivity to serum calcium.[32] Under normal conditions, an increase in calcium of approximately 1.2 mmol above the physiological set point appears sufficient to stimulate an immediate secretory response.

The released hormone subsequently appears to act both on the gill and on the gut epithelial cells to reduce calcium uptake. Within the fish kidney, STC functions to increase the tubular reabsorption of phosphate, to chelate and remove extracellular calcium.[33]

Does STC-1 Have a Role in Human Calcium or Phosphate Homeostasis?

Experiments involving the injection of human STC-1 into fish show that it can act as an antihypercalcemic factor, just as the native fish STC.[18,34] This suggests that the differences in amino acid sequence do not noticeably change the tertiary structure of the hormone between species, and therefore it is still able to exert the effect of the native hormone. The highly conserved amino acid sequence between species suggests a conserved physiological function across both fish and mammalian species.

An early putative role of STC-1 was thought to be in human calcium homeostasis or phosphate homeostasis. Experiments in rats injected with recombinant human STC-1 appear to disprove this hypothesis. When rats were injected with recombinant human STC-1, no effect on urinary calcium excretion or serum calcium levels were seen.[19] However, this result may have been due to PTH being a potent antihypocalcemic hormone that would be released by the parathyroid gland in rats in response to the expected hypokalemia induced by STC-1, not present in the bony fish that STC was originally discovered in. Furthermore, chronic elevations in serum STC-1 in transgenic mice have been shown to significantly alter serum levels of calcium and/or phosphate.[20,35]

The same experiment showed that renal phosphate excretion appeared to increase; however, the change measured in urinary phosphate was marginal and not dose-dependent; and did not affect the plasma concentration of phosphate.[19] This suggests that the result may be due to an experimental anomaly, and no crucial role for STC-1 in human phosphate excretion in the kidney has been directly observed.

However, this leaves open the possibility that PTH and STC-1 serve antagonistic roles; PTH as an antihypocalcemic system and STC-1 (along with calcitonin) as an antihypercalcemic system. A precedent for this has been reported in the regulation of blood pressure by neprilysin and angiotensin, with neprilysin acting as an antihypertensive and angiotensin as an antihypotensive mechanism. Evidence for this includes the fact that STC-1 can still bind to and act upon receptors to decrease calcium levels when examined in model systems where no parathyroid gland exists. In rat and swine duodenal tissue, the addition of recombinant human STC-1 increased calcium flux into the lumen with a subsequent reduction in calcium absorption from this gut tissue, and stimulated the absorption of phosphate in gut tissue from both of these species.[36]

STC-1 is Associated With Kidney Protection in Many Models of Kidney Disease

STC-1 has been shown to protect the kidneys across several disease states. In some recent studies, it has been reported that STC-1 has antioxidant, anti-inflammatory, and antiapoptotic activities,[37] playing a role in kidney protection in diseases which include

Table 1. Studies of stanniocalcin-1 and kidney disease

Author, year	Model	Findings
Liu *et al.*[38]	Mouse model	STC-1 as a regulator of AMPK, UCP2, and SIRT3 in the kidney
Huang *et al.*[39]	Mouse model	STC-1 inhibits macrophages, stabilizes endothelial barrier function, and diminishes trans-endothelial migration of leukocytes; transgenic (Tg) overexpression of STC-1 protects from nephrotoxic nephritis
Jepsen *et al.*[40]	Human tissues	Endogenous inhibited complexes of PAPP-A (PAPP-A:STC-1 and PAPP-A:STC-2) were demonstrated in media conditioned by human mesangial cells (HMCs), suggesting that PAPP-A activity is regulated by the STCs in kidney tissue. Significant increase in glomerular active PAPP-A in human diabetic kidney relative to normal was observed.
Zhao *et al.*[41]	Cell culture and rat model	Protective role of STC-1 in contrast-induced injury in cultured renal tubular epithelial cells and CI-AKI rat models. Recombinant human STC-1 regulated mitochondrial quality control, thus suppressing contrast-induced mitochondrial damage, oxidative stress, inflammatory response, and apoptotic injury. Mechanistically, activation of the Nrf2 signaling pathway contributes critically to the renoprotective effect of STC-1
Pan *et al.*[42]	Mouse model, cultured HEK cells	High AMPK activity in STC-1 transgenic kidneys relative to wild-type (WT) kidneys. Functional experiments showed STC-1 is important for activation of AMPK in the kidney, which mediates STC-1–induced expression of UCP2 and sirtuin 3 and protection from ischemic-reperfusion.

AMPK, AMP-activated protein kinase; SIRT3, sirtuin 3; STC-1, stanniocalcin-1; UCP2, uncoupling protein 2.

diabetic nephropathy in a mouse model. The studies on the renal effects of STC-1 are listed in Table 1.[38–42]

The Protective Role of STC-1 in the Development of Diabetic Nephropathy

As previously discussed, the prevalence of diabetes in patients with end-stage renal disease is 40%, and diabetic kidney disease is by far the most common cause of CKD.[4] One study directly examined the role of STC-1 in the development of diabetic nephropathy, showing that increased activity of the metalloprotease PAPP-A promoted diabetes-induced glomerular hypertrophy. PAPP-A is an activator of IGF activity. A significant increase in glomerular active PAPP-A in the human diabetic kidney was detected compared to normal kidney within tissue samples through immunohistochemistry. In patients with diabetic nephropathy, the level of PAPP-A in the plasma is increased.

STC-1 and STC-2 are endogenous inhibitors of this PAPP-A enzyme. Adenovirus-mediated overexpression of STC-2 in a mouse model prevented diabetes-related glomerular growth, compared to overexpression of a noninhibiting STC-2 mutant peptide. The authors concluded that STC overexpression again prevented deterioration of glomerular filtration rates due to diabetic nephropathy through this interaction with PAPP-A.[40]

The Protective Role of STC-1 in Ischemic and Reperfusion Injury to the Kidney, Which May Arise as a Consequence of Cardiovascular Morbidity

Ischemic injuries are common in conditions that are associated with cardiovascular disease, such as diabetes. Atherosclerosis results in poor circulation to various organs including the kidney. As previously discussed, patients who experience diabetic kidney disease also have poorer outcomes and more complications following treatments such as a percutaneous coronary intervention.[6]

Several studies have shown that STC-1 inhibits renal ischemia-reperfusion injury via an AMP-activated protein kinase–dependent pathway; and 1 study reported that AMP-activated protein kinase regulates the expression of uncoupling protein 2 and sirtuin 3, resulting in kidney protection.[38,42] It was hypothesized that STC-1 delays the progression of diabetic nephropathy also through inhibiting reactive oxygen species production through sirtuin upregulation. This AMP-activated protein kinase–dependent mechanism of hypoxia protection has also been reported in other organ systems, e.g., astrocytes.[43]

The hormone has also been shown to inhibit macrophages; findings from overexpressing STC-1 in transgenic mice resulted in a reduction in nephrotoxic nephritis, whereas a conditional and kidney-specific knockout of STC-1 resulted in severe nephrotoxic nephritis.[39]

Finally, 1 study used a rat model to demonstrate the effects of STC-1 in reducing the mitochondrially-driven reactive oxygen species production that results in contrast-induced nephropathy.[41]

The potential receptor that STC-1 binds to, has been identified as membrane protein receptor, MPRI also known as IGF 2 receptor found in many mammalian cells, which is known to regulate cell growth.[44] The role of STC-1 in promoting mitochondrial antioxidant activity has been identified to be dependent on the interaction of STC-1 signal peptide with tri leucines (L12–14) of the megalin protein.[45]

STC-1 has Been Associated With Significant Cardiovascular Protective Effects

The impact of chronic hypercalcemia on vasculature is well-described and leads to calcium deposition within coronary arteries and progression of atherosclerosis.[46] Circulating calcium is a risk factor for vascular disease, and mutations in the calcium sensing receptor associated with small elevations in serum calcium are

Table 2. Studies on stanniocalcin-1 and cardiovascular disease

Author, year	Model	Findings
Reid *et al.*[47]	Meta-analysis of human population studies	Meta-analysis of 8 studies showed a hazard ratio of cardiovascular disease of 1.08 (1.04, 1.13) per SD of serum calcium.
Sheikh-Hamad *et al.*[48]	Cultured rat cardiomyocytes	Addition of STC-1 to the bath causes reversible inhibition of transmembrane calcium currents through L-channels, slowing their endogenous beating rate and diminishes the increase in intracellular calcium with each contraction.
Jiang *et al.*[49]	Rat model	After treating rats with STC-1, the cardiac function and structure of the rats were significantly improved following an ischemia-reperfusion injury. In addition, STC-1 reduced the expression of inflammatory factors and apoptosis levels in rat myocardium. Stimulation of STC-1 also improved the viability of cultured rat myocardial cells in vitro.
Mohammadipoor *et al.*[50]	Human cell culture, mouse model	rSTC-1 treatment reduced CD14 expression in cultured human monocytes stimulated with endogenous danger signals. In mice with induced myocardial infarcts, i.v. administration of rSTC-1 decreased CD14 expression in the heart as well as levels of tumor necrosis factor alpha, C-X-C motif ligand 2, interleukin 1 β, and myeloperoxidase. It also suppressed the formation of scar tissue while enhancing cardiac function.

STC-1, stanniocalcin 1.

also significantly associated with cardiovascular disease.[47] Therefore, an antihypercalcemic system which may be mediated by STC-1 would serve to decrease the progression toward this atherosclerosis.

Furthermore, STC-1 has been found to be markedly upregulated within cardiomyocytes in cardiac tissue from patients with advanced heart failure, and this was markedly decreased after these patients had been fitted with a left-ventricular assist device. STC-1 appeared again to be cardioprotective, causing reversible inhibition of transmembrane calcium currents through L channels.[48] The addition of recombinant human STC-1 to cultured rat cardiomyocytes reduced the beating rate and reduced the increase in calcium associated with each contraction.

In addition, there have been numerous studies on the effect of STC-1 preconditioning in an ischemia-reperfusion model of the heart. One study showed that STC-1 alleviated myocardial ischemia-reperfusion injury through inhibition of inflammation and apoptosis of myocardial cells,[49] and another study showed STC-1 attenuating ischemic cardiac injury and the response of differentiating monocytes or macrophages to inflammatory stimuli, suppressing the formation of scar tissue while enhancing subsequent cardiac function.

The studies on cardiovascular and neurological effects of STC-1 are listed in Table 2.[47–49]

Conclusion

In the context of kidney and cardiovascular disease, STC-1 is a hormone released from the kidneys in response to hypercalcemia in both fish and mammals. Like in fish, STC-1 acts on the gut to reduce calcium absorption and increase phosphate absorption to chelate excess serum calcium.

Under normal physiology, serum STC-1 is undetectable; however, it increases in disease states, including heart failure and CKD. There is evidence it serves a protective role in both disease states, and further research to elucidate the link between the 2 diseases in humans may help in developing strategies to prevent the significant disease comorbidity shared between the 2 diseases.

In patients with diabetic kidney disease who experience multiple independent risk factors from their diabetes and their CKD to their cardiovascular health, and for whom cardiovascular disease is the largest factor in their mortality and morbidity, there is initial research to suggest that STC-1 serves an important role in the prevention of diabetic nephropathy as well as renoprotection in ischemia-reperfusion injury, and subsequent cardiovascular morbidity.

Future directions for research should include clinical studies on serum STC-1 and calcium levels in health and disease, to further elucidate the homeostatic role of this hormone. This research is especially important for patients with diabetic kidney disease because it may identify a mechanistic link between each of these risk factors and pave the way for future treatments to break this link and improve their quality of life.

DISCLOSURE

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REFERENCES

1. Schuster DP, Duvuuri V. Diabetes mellitus. *Clin Podiatr Med Surg*. 2002;19:79–107. https://doi.org/10.1016/S0891-8422(03)00082-X
2. Zghebi SS, Steinke DT, Carr MJ, Rutter MK, Emsley RA, Ashcroft DM. Examining trends in type 2 diabetes incidence, prevalence and mortality in the UK between 2004 and 2014. *Diabetes Obes Metab*. 2017;19:1537–1545. https://doi.org/10.1111/dom.12964
3. Saeedi P, Petersohn I, Salpea P, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the International Diabetes Federation Diabetes Atlas. *9th edition. Diabetes Res Clin Pract*. 2019;157:107843. https://doi.org/10.1016/j.diabres.2019.107843

4. Grăunţanu C, Moţa E, Moţa M, Panduru MN, Bîcu M, Vladu I. Cardiovascular risk in patients with diabetic kidney disease. *Rom J Intern Med Rev Roum Med Intern*. 2010;48:313–319.
5. Rocha NA, McCullough PA. Cardiovascular outcomes in diabetic kidney disease: insights from recent clinical trials. *Kidney Int Suppl (2011)*. 2018;(8):8–17. https://doi.org/10.1016/j.kisu.2017.10.004
6. Nikolsky E, Mehran R, Turcot D, et al. Impact of chronic kidney disease on prognosis of patients with diabetes mellitus treated with percutaneous coronary intervention. *Am J Cardiol*. 2004;94:300–305. https://doi.org/10.1016/j.amjcard.2004.04.023
7. Szczech LA, Best PJ, Crowley E, et al. Outcomes of patients with chronic renal insufficiency in the bypass angioplasty revascularization investigation. *Circulation*. 2002;105:2253–2258. https://doi.org/10.1161/01.cir.0000016051.33225.33
8. Wagner GF, Hampong M, Park CM, Copp DH. Purification, characterization, and bioassay of teleocalcin, a glycoprotein from salmon corpuscles of Stannius. *Gen Comp Endocrinol*. 1986;63:481–491. https://doi.org/10.1016/0016-6480(86)90149-8
9. Stannius H. Über Nebenniere bei Knochenfischen. *Arch Anat Physiol*. 1839;6:97–101.
10. Fontaine M. Stannius' corpuscles and ionic (CA, K, NA) of the interior environment of the eel (Anguilla anguilla L.). *Article in French. C R Hebd Seances Acad Sci*. 1964;259:875–878.
11. Lafeber FP, Hanssen RG, Choy YM, et al. Identification of hypocalcin (teleocalcin) isolated from trout Stannius corpuscles. *Gen Comp Endocrinol*. 1988;69:19–30. https://doi.org/10.1016/0016-6480(88)90048-2
12. Chang AC, Janosi J, Hulsbeek M, et al. A novel human cDNA highly homologous to the fish hormone stanniocalcin. *Mol Cell Endocrinol*. 1995;112:241–247. https://doi.org/10.1016/0303-7207(95)03601-3
13. Chang AC, Reddel RR. Identification of a second stanniocalcin cDNA in mouse and human: stanniocalcin 2. *Mol Cell Endocrinol*. 1998;141:95–99. https://doi.org/10.1016/s0303-7207(98)00097-5
14. Ishibashi K, Imai M. Prospect of a stanniocalcin endocrine/paracrine system in mammals. *Am J Physiol Ren Physiol*. 2002;282:F367–F375. https://doi.org/10.1152/ajprenal.00364.2000
15. De Niu P, Radman DP, Jaworski EM, et al. Development of a human stanniocalcin radioimmunoassay: serum and tissue hormone levels and pharmacokinetics in the rat. *Mol Cell Endocrinol*. 2000;162:131–144. https://doi.org/10.1016/s0303-7207(00)00199-4
16. Deol HK, Varghese R, Wagner GF, Dimattia GE. Dynamic regulation of mouse ovarian stanniocalcin expression during gestation and lactation. *Endocrinology*. 2000;141:3412–3421. https://doi.org/10.1210/endo.141.9.7658
17. Song H, Xu B, Yi J. Clinical significance of stanniocalcin-1 detected in peripheral blood and bone marrow of esophageal squamous cell carcinoma patients. *J Exp Clin Cancer Res*. 2012;31:35. https://doi.org/10.1186/1756-9966-31-35
18. Wagner GF, Guiraudon CC, Milliken C, Copp DH. Immunological and biological evidence for a stanniocalcin-like hormone in human kidney. *Proc Natl Acad Sci U S A*. 1995;92:1871–1875. https://doi.org/10.1073/pnas.92.6.1871
19. Wagner GF, Vozzolo BL, Jaworski E, et al. Human stanniocalcin inhibits renal phosphate excretion in the rat. *J Bone Miner Res*. 1997;12:165–171. https://doi.org/10.1359/jbmr.1997.12.2.165
20. Varghese R, Gagliardi AD, Bialek PE, Yee SP, Wagner GF, Dimattia GE. Overexpression of human stanniocalcin affects growth and reproduction in transgenic mice. *Endocrinology*. 2002;143:868–876. https://doi.org/10.1210/endo.143.3.8671
21. Sheikh-Hamad D. Mammalian stanniocalcin-1 activates mitochondrial antioxidant pathways: new paradigms for regulation of macrophages and endothelium. *Am J Physiol Ren Physiol*. 2010;298:F248–F254. https://doi.org/10.1152/ajprenal.00260.2009
22. Trindade DM, da Silva JC, Navarro MS, Torriani IC, Kobarg J. Low-resolution structural studies of human Stanniocalcin-1. *BMC Struct Biol*. 2009;9:57. https://doi.org/10.1186/1472-6807-9-57
23. Chang ACM, Jellinek DA, Reddel RR. Mammalian stanniocalcins and cancer. *Endocr Relat Cancer*. 2003;10:359–373. https://doi.org/10.1677/erc.0.0100359
24. Paciga M, Hirvi ER, James K, Wagner GF. Characterization of big stanniocalcin variants in mammalian adipocytes and adrenocortical cells. *Am J Physiol Endocrinol Metab*. 2005;289:E197–E205. https://doi.org/10.1152/ajpendo.00581.2004
25. Jellinek DA, Chang AC, Larsen MR, Wang X, Robinson PJ, Reddel RR. Stanniocalcin 1 and 2 are secreted as phosphoproteins from human fibrosarcoma cells. *Biochem J*. 2000;350:453–461. https://doi.org/10.1042/bj3500453
26. Joshi AD. New insights into physiological and pathophysiological functions of Stanniocalcin 2. *Front Endocrinol*. 2020;11:172. https://doi.org/10.3389/fendo.2020.00172
27. Luo CW, Pisarska MD, Hsueh AJW. Identification of a Stanniocalcin paralog, stanniocalcin-2, in fish and the paracrine actions of Stanniocalcin-2 in the mammalian ovary. *Endocrinology*. 2005;146:469–476. https://doi.org/10.1210/en.2004-1197
28. Schein V, Cardoso JCR, Pinto PIS, et al. Four stanniocalcin genes in teleost fish: structure, phylogenetic analysis, tissue distribution and expression during hypercalcemic challenge. *Gen Comp Endocrinol*. 2012;175:344–356. https://doi.org/10.1016/j.ygcen.2011.11.033
29. Bishop A, Cartwright JE, Whitley GS. Stanniocalcin-1 in the female reproductive system and pregnancy. *Hum Reprod Update*. 2021;27:1098–1114. https://doi.org/10.1093/humupd/dmab028
30. Moore EE, Kuestner RE, Conklin DC, et al. Stanniocalcin 2: Characterization of the protein and its localization to human pancreatic alpha cells. *Horm Metab Res*. 1999;31:406–414. https://doi.org/10.1055/s-2007-978764
31. Radman DP, McCudden C, James K, Nemeth EM, Wagner GF. Evidence for calcium-sensing receptor mediated stanniocalcin secretion in fish. *Mol Cell Endocrinol*. 2002;186:111–119. https://doi.org/10.1016/s0303-7207(01)00643-8
32. Greenwood MP, Flik G, Wagner GF, Balment RJ. The corpuscles of Stannius, calcium-sensing receptor, and stanniocalcin: responses to calcimimetics and physiological challenges. *Endocrinology*. 2009;150:3002–3010. https://doi.org/10.1210/en.2008-1758

33. Gerritsen ME, Wagner GF. Stanniocalcin: no longer just a fish tale. *Vitam Horm*. 2005;70:105–135. https://doi.org/10.1016/S0083-6729(05)70004-2
34. Olsen HS, Cepeda MA, Zhang QQ, Rosen CA, Vozzolo BL, Wagner GF. Human stanniocalcin: a possible hormonal regulator of mineral metabolism. *Proc Natl Acad Sci U S A*. 1996;93:1792–1796. https://doi.org/10.1073/pnas.93.5.1792
35. Filvaroff EH, Guillet S, Zlot C, et al. Stanniocalcin 1 alters muscle and bone structure and function in transgenic mice. *Endocrinology*. 2002;143:3681–3690. https://doi.org/10.1210/en.2001-211424
36. Madsen KL, Tavernini MM, Yachimec C, et al. Stanniocalcin: a novel protein regulating calcium and phosphate transport across mammalian intestine. *Am J Physiol Gastrointest Liver Physiol*. 1998;274:G96–G102. https://doi.org/10.1152/ajpgi.1998.274.1.G96
37. Liu D, Shang H, Liu Y. Stanniocalcin-1 protects a mouse model from renal ischemia-reperfusion injury by affecting ROS-mediated multiple signaling pathways. *Int J Mol Sci*. 2016;17:1051. https://doi.org/10.3390/ijms17071051
38. Liu Z, Liu H, Xiao L, Liu G, Sun L, He L. STC-1 ameliorates renal injury in diabetic nephropathy by inhibiting the expression of BNIP3 through the AMPK/SIRT3 pathway. *Lab Investig*. 2019;99:684–697. https://doi.org/10.1038/s41374-018-0176-7
39. Huang L, Lou Y, Ju H, et al. Severe Nephrotoxic Nephritis following Conditional and Kidney-Specific Knockdown of Stanniocalcin-1. *PLoS One*. 2015;10:e0138440. https://doi.org/10.1371/journal.pone.0138440
40. Jepsen MR, Østergaard JA, Conover CA, et al. Increased activity of the metalloproteinase PAPP-A promotes diabetes-induced glomerular hypertrophy. *Metab Clin Exp*. 2022;132:155218. https://doi.org/10.1016/j.metabol.2022.155218
41. Zhao F, Feng LX, Liu Q, et al. Stanniocalcin-1 alleviates contrast-induced acute kidney injury by regulating mitochondrial quality control via the Nrf2 pathway. *Oxid Med Cell Longev*. 2020;2020:1898213. https://doi.org/10.1155/2020/1898213
42. Pan JSC, Huang L, Belousova T, et al. Stanniocalcin-1 inhibits renal ischemia/reperfusion injury via an AMP-activated protein kinase-dependent pathway. *J Am Soc Nephrol*. 2015;26:364–378. https://doi.org/10.1681/ASN.2013070703
43. Sun B, He S, Liu B, et al. Stanniocalcin-1 protected astrocytes from hypoxic damage through the AMPK pathway. *Neurochem Res*. 2021;46:2948–2957. https://doi.org/10.1007/s11064-021-03393-z
44. Wan HT, Ng AH, Lee WK, Shi F, Wong CKC. Identification and characterization of a membrane receptor that binds to human STC1. *Life Sci Alliance*. 2022;5:e202201497. https://doi.org/10.26508/lsa.202201497
45. Li Q, Holliday M, Pan JS, Tan L, Li J, Sheikh-Hamad D. Interactions between leucines within the signal peptides of megalin and stanniocalcin-1 are crucial for regulation of mitochondrial metabolism. *Lab Investig*. 2022;102:534–544. https://doi.org/10.1038/s41374-022-00729-3
46. Roberts WC, Waller BF. Effect of chronic hypercalcemia on the heart. An analysis of 18 necropsy patients. *Am J Med*. 1981;71:371–384. https://doi.org/10.1016/0002-9343(81)90163-7
47. Reid IR, Gamble GD, Bolland MJ. Circulating calcium concentrations, vascular disease and mortality: a systematic review. *J Intern Med*. 2016;279:524–540. https://doi.org/10.1111/joim.12464
48. Sheikh-Hamad D, Bick R, Wu GY, et al. Stanniocalcin-1 is a naturally occurring L-channel inhibitor in cardiomyocytes: relevance to human heart failure. *Am J Physiol Heart Circ Physiol*. 2003;285:H442–H448. https://doi.org/10.1152/ajpheart.01071.2002
49. Jiang X, Zhao D, Stanniocalcin BLJ. Stanniocalcin 1 alleviates myocardial ischemia-reperfusion injury through inhibiting inflammation and apoptosis of myocardial cells. *Eur Rev Med Pharmacol Sci*. 2022;26:4309–4317. https://doi.org/10.26355/eurrev_202206_29070
50. Mohammadipoor A, Lee RH, Prockop DJ, Bartosh TJ. Stanniocalcin-1 attenuates ischemic cardiac injury and response of differentiating monocytes/macrophages to inflammatory stimuli. *Transl Res*. 2016;177:127–142. https://doi.org/10.1016/j.trsl.2016.06.011