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CARDIOTROPHIN-1 REVIEW

David Stejskal[a, b]*, Viktor Ruzicka[c]

[a] *Department of Laboratory Medicine and Department of Internal Medicine, Šternberk Hospital, Czech Republic*
[b] *Department of Medical Chemistry and Biochemistry, Faculty of Medicine and Dentistry, Palacky University, 775 15 Olomouc, Czech Republic*
[c] *BioVendor Laboratory Medicine, Brno, Czech Republic*
e-mail: biodast@seznam.cz

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Key words: Acute Coronary Syndromes/Metabolic Syndrome/Cardiovascular Diseases/ Cancers/Laboratory markers/Cardiotrophin-1/ELISA

Background: Cardiotrophin-1 is newly discovered chemokin with a lot of functions. Aim of our work was to describe most important of them.

Methods: systematically scan of available scientific resources.

Results: Cardiotrophin-1 stimulates the proliferation of cardiomyocytes. Cardiotrophin-1 expression and plasma values are elevated in individuals with heart failure and have high diagnostic efficacy for the heart failure. Plasma values are also an independent prognostic factor. Preliminary findings suggest that the determination of plasma cardiotrophin-1 may be useful for the follow-up of hypertensive heart disease in routine clinical practice. Cardiotrophin-1 also plays an important cardioprotective effect on myocardial damage, is a potent regulator of signaling in adipocytes in vitro and in vivo and potentiates the elevation the acute-phase proteins. Cardiotrophin-1 may play also an important protective role in other organ systems (such as hematopoietic, neuronal, developmental).

Conclusion: Cardiotrophin is a newly discovered chemokin with a lot of system effects and is stable in system circulation hence permitting its development in the routine clinical investigation.

INTRODUCTION

Cardiotrophin-1 (CT-1) is recently discovered substance which affected most of organ systems. CT-1 is stable in specimens of whole blood treated with EDTA and aprotinin and stored for up to 48 hours at room temperature or on ice, hence permitting its development in the routine clinical investigation[48]. Aim of our work was to describe most important effects on body tissues and organ systems.

Cardiotrophin 1 molecule

Expression cloning lead to the isolation of a 21.5 kDa protein, named cardiotrophin-1 CT-1), that potently induced cardiac myocyte hypertrophy in vitro. Amino acid similarity data indicate that cardiotrophin-1 is a member of the leukemia inhibitory factor/ciliary neurotrophic factor/oncostatin M/interleukin 6/interleukin 11 family of cytokines. Several members of this family that are known to signal through the transmembrane protein gp130 and stimulate pathways. Cross-linking of iodinated CT-1 to the cell surface led to the identification of a third alpha component in addition to gp130 and gp190, with an apparent molecular mass of 80 kDa. cardiac myocyte hypertrophy, like cardiotrophin 1, suggesting that the gp130 signaling pathway may play a role in cardiac hypertrophy. The 1.4-kb CT-1 mRNA is expressed in the heart and several other mouse tissues[1]. In mice, after day 12.5 postconception, CT-1 expression is found in skeletal muscle, liver and dorsal root ganglia[6]. The 1.7 kb CT-1 mRNA is expressed in adult human heart, skeletal muscle, ovary, colon, prostate and testis and in fetal kidney and lung. The coding region of CT-1 is contained on three exons and is located on human chromosome 16p11.1-16p11.2 (ref.[9]). The expression pattern of CT-1 and its range of activities in the hematopoietic, neuronal, and developmental assays suggest that CT-1 may play an important role in other organ systems, in addition to its actions in cardiac development and hypertrophy[11].

Cardiotrophin-1 receptor

Gp130-gp190 heterocomplex formation is essential for CT-1 signaling. Analysis of the subsequent activation events revealed that CT-1 induces and utilizes Jak1-, Jak2-, and Tyk2-associated tyrosine kinases, which are in turn relayed by STAT-3 transcription factor and MAPK (ERK1 and -2) signaling Removal of N-linked carbohydrates from the protein backbone of the alpha component resulted in a protein of 45 kDa. These results provide evidence that the CT-1 receptor is composed of a tripartite complex, a situation similar to the high affinity receptor for ciliary neurotrophic factor[15]. Results indicate that gp130 plays a crucial role in myocardial development and hematopoiesis during embryogenesis[5, 106].

Factors regulating CT-1 expression and regulated by CT-1 are presented in tables 1 and 2.

Table 1. Factors regulating CT-1 expression.

Angiotensin II	↑↑ IL-6, LIF, and CT-1 in cardiac fibroblasts. CT-1 ↑↑ angiotensinogen mRNA expression in cardiac myocytes. Upregulation of angiotensinogen and angiotensin II production contribute to CT-1-induced cardiac myocyte hypertrophy[35]
Norepinephrine	↑↑ the expression of CT-1 mRNA in cardiac myocytes, both in vivo and in vitro[36]
Urocortin	↑↑ expression of CT-1 at both the mRNA and protein levels[76]
Fibroblast growth factor 2 (FGF-2)	Hmw- FGF-2 – ↑↑ upregulation of CT-1 in cardiomycytes and causes post-MI hypertrophy[104]
Glucose and Insulin	↑↑ CT and is inhibited effects of pioglitazone (on myocardial hypertrophy)[121]
Reactive oxygen species	↑↑ CT expression

Table 2. Factors regulated by CT-1.

HSP	CT-1 ↑↑ synthesis of the heat shock proteins hsp70 and hsp90. Such CT-1-treated cells are protected against subsequent exposure to severe thermal or ischaemic stress. Pre-treatment with CT-1 reduces the ability of heat shock to induce hsp expression. CT-1 ↑↑ Hsp56 at both the mRNA and protein levels. Overexpression of hsp56 caused a significant increase in cardiac cell size and protein:DNA ratio. Thus, a hypertrophic effect has been demonstrated for a hsp and demonstrates that CT-1-induced hypertrophy involves a specific hsp, which is not involved in its protective effect[43, 53, 82]
P53, Fas, Bax, Bcl2-	CT-1 ↓↓ P53, Fas and Bax, and ↑↑ Bcl-2 expression in myocardium
Interleukin-6 (IL-6)	CT-1 ↑↑ a concentration- and time-dependent increase in IL-6 mRNA and protein concentration. There is speculated that in chronique heart failure CT-1 might be in part responsible for increased IL-6 plasma concentrations[108]
STAT1, -3, -5A, -5B, ERK1 and -2	CT-1 ↑↑activation and nuclear translocation of STAT- 1, 3, 5a and 5b as well as ERK1 and -2
MCP1	CT-1 ↑↑ a concentration and time dependent manner MCP-1 mRNA; STAT3 phosphorylation, the activation of JAK2 and NF-kappaB are involved in this pathway[100]
Fatty acid synthese and Substrate-1 protein expression	CT-1 ↓↓ of fatty acid synthase and insulin receptor substrate-1 protein expression

CT-1 Signalling

Gp130 is required for CT-1 signaling in cardiomyocytes, by demonstrating that a monoclonal anti-gp130 antibody completely inhibits c-fos induction by CT-1. Similarly, a leukemia inhibitory factor receptor subunit beta (LIFR-β) antagonist effectively blocks the CT-1 induction of c-fos, indicating a requirement for LIFR-β in the hypertrophic response, as well. Upon stimulation with CT-1, both gpl30 and the LIFR-β are tyrosine-phosphorylated, providing further evidence that CT-1 signals through the gp130/LIFR-β heterodimer in cardiomyocytes[10]. CT-1 promotes cardiac myocyte survival via the activation of an antiapoptotic signaling pathway that requires MAP kinases, whereas the hypertrophy induced by CT-1 may be mediated by alternative pathways, e.g. Janus kinase/STAT or MEK kinase/c-Jun NH2-terminal protein kinase[16, 30]. A more recent study concluded that STAT3 transduces not only a hypertrophic signal but also a protective signal against doxorubicine-induced cardiomyopathy by inhibiting reduction of cardiac contractile genes and inducing cardiac protective factors. Hypertrophic effect of CT-1 was essentially mediated by STAT3, independent of PI3-K, and negatively regulated by ERK1/2 via inhibiting the phosphorylation of STAT3. The interaction between STAT3 and ERK1/2 in CT-1-induced signaling contributes to development of cardiac hypertrophy[31, 87, 89]. New findings also indicate that the major pathway responsible for the hypertrophic responses to CT-1 is not JAK-STAT3 pathway nor MEK1-ERK1/2 pathway, but MEK5-ERK5 pathway[49, 90]. In vivo, the death of ventricular myocytes leads to heart failure, and downregulation of survival signals and/or augmentation of pro-apoptotic signals are likely to be important components of disease processes. Thus, the extent to which CT-1 and the PI3K/Akt path-

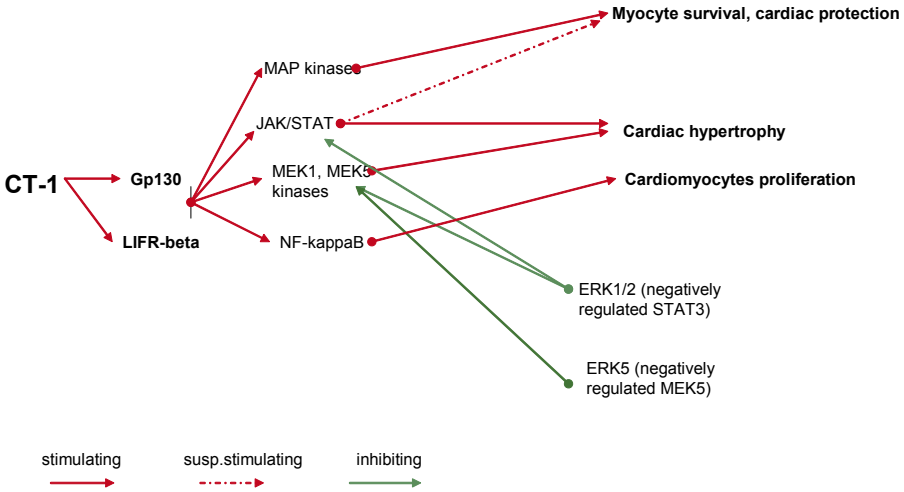

Fig. 1. CT-1 signaling.

way mitigate such pathological processes, in vivo, is an important question for the future[39]. CT-1 activated also nuclear factor-kappaB (NF-kappaB). It seems that CT-1 stimulates the proliferation of cardiomyocytes by signaling pathways that involve ROS as signaling molecules in the signal transduction cascade[83] (Fig. 1).

Clinical statuses and CT-1

Congestive heart failure (CHF)

A significant increase in the plasma CT-1 concentration from the aorta and coronary sinus was described, which clearly indicates that the heart secretes CT-1 via the coronary sinus into the peripheral circulation[45]. Both CT-1 and B-type natriuretic peptide (BNP) are activated by cardiomyocyte stretch, and gene expression of CT-1 and BNP are augmented in the heart in experimental and human CHF. CT-1 mRNA was detected in both atria and ventricles. Differential regulation of gene expression of CT-1 and BNP in the heart during the progression of CHF demonstrates that ventricular CT-1 gene activation precedes ventricular BNP gene activation[75]. Ventricular CT-1 mRNA correlates with left ventricular hypertrophy, suggesting that CT-1 plays an important role in the structural remodeling that characterizes CHF[32]. In the failing human left ventricular myocardium, expression levels of CT-1 mRNA and protein were significantly increased by 142 % and 68 %, respectively, compared with non-failing donor hearts. Although gp130 gene expression was increased by 91 %, gp130 protein abundance was significantly diminished by 34 % in the failing myocardium. In contrast, leukemia inhibitory factor receptor (LIF-R) and suppressor of cytokine signaling-3 (SOCS3) protein concentrations were not changed. These data suggest that gp130 receptor downregulation balances enhanced CT-1 expression in human heart failure and thereby inhibits excessive activation of the gp130 signaling pathway[69]. CT-1 may be able to induce MCP-1 which might be responsible for progression of heart failure either by recruiting inflammatory cells within the myocardium or by a direct modulation of myocyte function[100].

In patients with left ventricular systolic dysfunction (LVSD), CT-1 plasma levels was elevated compared with controls. Log CT-1 was correlated with log wall motion index, log left ventricular end-systolic volume, stroke volume and log fractional shortening. In a multivariate model of the predictors of log wall motion index, the only significant predictor was log CT-1. This demonstrates that CT-1 is elevated in heart failure in relation to the severity of LVSD[25, 37].

Plasma CT-1 has high diagnostic efficacy for heart failure (at concentration of 68 fmol/ml, sensitivity and specificity were 95 % and 82.5 % respectively[64]). Patients with chronique kidney disease (CHKD) having left ventricular hypertrophy (LVH) have also higher plasma levels CT-1 than individuals CHKD without LVH[110].

CT-1 and gp130 is overexpressed the heart during acute Chagasic Carditis. Their overexpression may provide a mechanism for myocyte protection, and for development of compensatory cardiac hypertrophy following myocardial damage in this form of cardiomyopathy[22].

Prognosis of CHF

Prognostic significance was assessed using the measurement the plasma levels of CT-1, BNP, and IL-6 in 125 patients with CHF. Patients were monitored for a mean follow-up period of 2.9 years. Plasma levels of CT-1 increased with severity of CHF. There was a significant negative correlation between plasma CT-1 and left ventricular ejection fiction (LVEF). There was a significant correlation between plasma CT-1 and log IL-6. High plasma levels of CT-1, BNP, and IL-6 were independent predictors of mortality on stepwise multivariate analysis. The hazard ratio for mortality in patients with plasma BNP > 170 pg/mL and CT-1>658 fmol/mL was 2.48 compared to those with plasma BNP>170 pg/mL and CT-1<658 fmol/mL. These findings indicate that plasma CT-1 measurement provides additional prognostic information and that combined levels of CT-1 and BNP are more accurate at predicting mortality in patients with CHF than either marker alone[114].

Dilated cardiomyopathy (DCM)

The plasma CT-1 level was increased in DCM patients with the severity of CHF and was significantly higher in

the large left ventricular (LV) mass group than in the small LV mass group, despite the absence of a difference in LV ejection fraction between the two groups. In addition, there was a significant positive correlation between the plasma CT-1 level and the LV mass index. According to stepwise multivariate analyses among hemodynamic and neurohumoral factors, a high plasma CT-1 level showed an independent and significant positive relationship with a large LV mass index in patients with DCM. These results indicate that CT-1 plays an important role in structural LV remodeling in patients with DCM[57].

Hypertension

In a study involving rats, atrial tissue concentrations of CT-1 were 8-fold higher than ventricular levels[95].

Dahl salt-sensitive (DS) rats with a high-salt diet showed a distinct transition from left ventricular hypertrophy (LVH) to congestive heart failure (CHF). The expression levels of CT-1 mRNA and protein were significantly increased at the CHF stage compared with the LVH stage and age-matched Dahl salt-resistant (DR) rats[62]. The expression of cardiotrophin-1 mRNA is increased in the early stage of ventricular hypertrophy in rats and it remains elevated after hypertrophy. However, it is unlikely that cardiotrophin-1 plays a mechanistic role in the development and maintenance of left ventricular hypertrophy in rats[7, 26, 94, 112].

Plasma levels of CT-1 in patients with untreated hypertension (UTH) were significantly higher than those in age-and BMI-matched normotensive volunteers. CT-1 levels in matched patients with treated hypertension were similar to those in UTH patients, but higher than in normotensive controls. Plasma CT-1 demonstrated a weak but significant correlation with systolic blood pressure in all patients[95]. Another study was performed in patients with never-treated hypertension and without prevalent cardiac disease. A direct correlation was found between CT-1 and observed left ventricular mass/predicted left ventricular mass ratio in all hypertensive patients. After treatment, plasma CT-1 decreased and increased in patients in which inappropriate left ventricular mass regressed and persisted, respectively, despite a similar reduction of blood pressure in the 2 subgroups of patients. Final values of CT-1 were inversely correlated with the decrease in the left ventricular mass index (LVMI) after treatment in all patients. These results suggest the hypothesis that an excess of CT-1 may contribute to inappropriate left ventricular growth in hypertensive patiens and show an association between treatment-induced decrease of plasma CT-1 and LVH regression in essential hypertension[115]. Although preliminary, these findings suggest that the determination of plasma CT-1 may be useful for the follow-up of hypertensive heart disease in routine clinical practice[99, 115].

Valvular disease

Plasma CT-1 is raised in those patients with moderate/severe mitral regurgitation in the presence of normal left ventricular systolic function. This secretion of CT-1 could potentially be the cause of ventricular dilatation and subsequent loss of contractile function in these patients. It also offers the intriguing possibility that plasma CT-1 could be used to monitor progression of mitral regurgitation biochemically[44].

Another study compared plasma NT-proBNP and CT-1 in aortic stenosis (AS) patiens. CT-1 levels were elevated in AS patients when compared with the controls. These results suggest NT-proBNP and CT-1 could potentially be used to monitor progression of disease non-invasively. These markers may also be useful to identify the optimum time for surgery in AS[47].

Myocardial Hypoxia

CT-1 expression is augmented after hypoxic stimulation and hypoxic conditioned medium presented enhanced ability to activate STAT3 in cardiac myocytes. Thus, CT-1 might play an important role in the pathogenesis of ischemic heart disease[29]. It was shown that prooxidants and physiological hypoxia increased CT-1 as well as HIF-1α–protein and mRNA expression in embryoid bodies, indicating that CT-1 expression is regulated by reactive oxygen species (ROS) and hypoxia. Treatment with prooxidants increased gp130 phosphorylation and protein expression of NADPH oxidase subunits p22-phox, p47-phox, p67-phox, as well as Nox1 and Nox4 mRNA. Prooxidants activated ERK1,2, JNK and p38 as well as PI3-kinase. Results demonstrate that CT-1 expression s is regulated by ROS and HIF-1-α and imply a crucial role of CT-1 in the survival and proliferation of cardiac cells[101].

In another study, CT-1 concentration was 142.5 fmol/ml in unstable angina, 73.2 fmol/ml in stable angina, and 27 fmol/ml in controls ($p < 0.01$). Log CT-1 correlated with log NT-proBNP in unstable angina. Both circulating NT-proBNP and CT-1 are raised in unstable angina, while CT-1 alone is raised in stable angina. The role of CT-1 and the relation between CT-1 and N-BNP in myocardial ischaemia remain to be defined[40].

CT-1 upregulation in the course of myocardial infarction

CT-1 and gp130 mRNA levels increased in rats with myocardial infarct at 1, 3, 7, 14, 28 and 56 days post-infarct in the infarct area, the ventricular septum (non-infarcted area) and right ventricle. Also the protein levels of CT-1

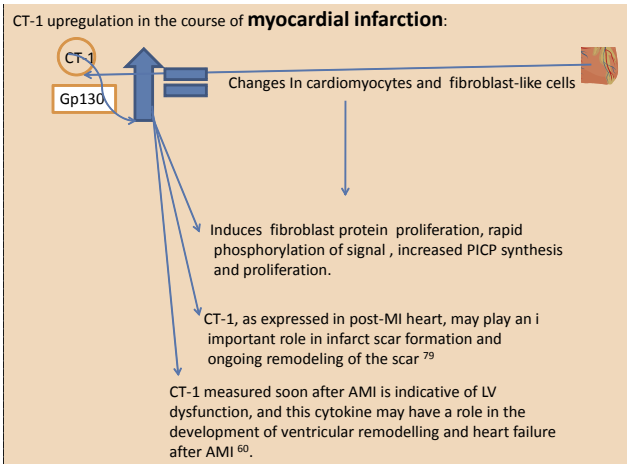

Fig. 2. Effect of CT-1 in myocardial infarct and ischemiea

and gp130 were significantly increased, peaked during the acute stage and declined thereafter in the three regions described above, CT-1 effects is descibed at Figure 2.

Prognosis of heart failure and death after AMI

Plasma CT-1 predicted death or heart failure independently of age, sex, previous AMI, serum creatinine, and Killip class, similarly as NT-proBNP. After an AMI, combined levels of CT-1 and NT-proBNP are more informative at predicting death or heart failure than either marker alone[103].

CT-1 protects the heart from the consequences of ischemia

CT-1 pretreatment in rats with left coronary ligation did not affect the heart rate, heart weight, body weight or the ratio of heart weight to body weight. The number of apoptotic cardiomyocytes in CT-1 treated group was less than that in control group. CT-1 pretreatment significantly inhibited P53, Fas and Bax, and increased Bcl-2 expression in myocardium[81]. A recent studies observed the effect of CT-1 on cardiomyocytes in an animal model of myocardial infarction. Results suggest that CT-1 plays an important cardioprotective effect on myocardial damage[43, 119].

CT-1 can exert a protective effect against the damaging effects of simulated ischaemia/reoxygenation both when added after the simulated ischaemia at reoxygenation or when added prior to the simulated ischaemia. In both cases, these protective effects are blocked by an inhibitor of the p42/p44 MAPK pathway. Hence CT-1 may have therapeutic potential when added at the time of reperfusion following ischaemic damage[55]. Taken together, CT-1 can protect adult cardiac cells both in vitro and in vivo when added both prior to or after the hypoxic/ischaemic stimulus[65].

CT-1 in Cardiac Non-myocytes and cardiac hypertrophy

CT-1 secreted from cardiac nonmyocytes is significantly involved in the hypertrophic changes of cardiac myocytes in the coculture. It was shown that CT-1 is an important local regulator in the process of cardiac hypertrophy. CT-1 and its receptors are present in cardiac fibroblasts. Gp130/LIF receptor and ET(A) receptor activation are essential for cardiac fibroblast growth by CT-1 and that there is synergism with ET-1/ET(A) receptor axis[27, 63]. CT-1 activates the Jak/STAT, PI3K/Akt, p38 and p42/44 MAPK pathways in cardiac fibroblasts. Use of pharmacologic inhibitors reveals that each of these pathways play a role in CT-1 induced protein synthesis[78].

CT-1, Adipose Tissue and metabolic syndrome (MS)

Adipose tissue as a target for CT-1

CT-1 administration results in a dose- and time-dependent activation and nuclear translocation of STAT1, -3, -5A, and -5B as well as ERK1 and -2 in fat cells in vivo. However, acute CT-1 treatment caused an increase in SOCS3 mRNA in adipocytes and a transient decrease in peroxisome proliferator-activated receptor gamma (PPARgamma) mRNA that was regulated by the binding of STAT1 to the PPARgamma2 promoter. The effects of CT-1 on SOCS3 and PPARgamma mRNA were independent of MAPK activation. Chronic administration of CT-1 to 3T3-L1 adipocytes resulted in a decrease of both fatty acid synthase and insulin receptor substrate-1 protein expression yet did not effect the expression of a variety of other adipocyte proteins. Moreover, chronic CT-1 treatment resulted in the development of insulin resistance as judged by a decrease in insulin-stimulated glucose uptake. In summary, CT-1 is a potent regulator of signaling in adipocytes in vitro and in vivo[88].

Adipose tissue as a source of CT-1

CT-1 expression progressively increased along with differentiation time from preadipocyte to mature adipocyte in 3T3-L1 cells. CT-1 expression was enhanced by glucose in a dose-dependent manner in these cells. Finally, increased CT-1 serum levels were observed in patients with metabolic syndrome compared with control subjects. Circulating levels of CT-1 were associated with glucose levels. These data suggest that adipose tissue can be recognized as a source of CT-1, which could account for the high circulating levels of CT-1 in patients with MS[117].

CT-1 and Endothelium

CT-1 induces monocyte adhesion and migration by stimulating gene and protein expressions of ICAM-1 and MCP-1 in human aortic endothelial cells (HAECs). CT-1-mediated up-regulation of ICAM-1 and MCP-1 was suppressed by PD98059, SB203580, LY294002, and parthenolide. In was suggested that CT-1 plays an important role in the pathophysiology of vascular inflammation and atherosclerosis [118].

Cardiotrophin-1 and Endotoxin Burden

Concerning the Heart

CT-1 might play a protective role in some TNF-mediated diseases[13]. CT-1 potentiates the elevation of serum corticosterone and IL-6 levels induced by IL-1 and induces the acute-phase protein serum amyloid A[8]. The effect of CT-1 on lipopolysaccharide (LPS)-induced cardiac dysfunction was examined in a rat model of sepsis. In the absence of CT-1, LPS elicited a reduction of systolic function and dilation of the ventricular cavity within 3-6 h after administration. These physiological effects were accompanied by increased ventricular phosphorylation of STAT1 and STAT3, activation of nuclear factor-kappaB and expression of iNOS mRNA. Notably, administration of CT-1 immediately prior to LPS significantly inhibited all of these LPS-induced changes. Forced expression of SOCS1 significantly inhibited iNOS transcription induced by LPS, tumor necrosis factor-alpha or interferon-gamma. The data suggest that CT-1-mediated expression of SOCS1 in cardiomyocytes may be a useful target for preventing sepsis-induced myocardial depression[98].

Concerning the Lung

The effects of CT-1 in a rat model of endotoxin-induced (ETX) acute lung injury were studied. Six hours

after ETX, lungs were harvested for determination of neutrophil accumulation and lung edema. CT-1 abrogated the endotoxin-induced lung neutrophil accumulation in the ETX group. Similarly, CT-1 prevented ETX-induced lung edema. Endotoxin caused significant impairment of both endothelium-dependent and -independent pulmonary vasorelaxation, and CT-1 attenuated this injury. Thus, cardiotrophin-1 possesses significant anti-inflammatory properties in a model of endotoxin-induced acute lung injury[24].

CT-1 and the Liver diseases

CT-1 is up-regulated during liver regeneration and exerts potent antiapoptotic effects on hepatocytic cells. Treatment with an adenovirus encoding CT-1 efficiently protects rats against fulminant liver failure after subtotal hepatectomy. This protective effect was associated with reduced caspase-3 activity and activation of the antiapoptotic signaling cascades STAT3 , extracellular regulated kinases (Erk) 1/2, and Akt in the remnant liver. In conclusion, CT-1 is a hepatocyte survival factor that efficiently reduces hepatocellular damage in animal models of acute liver injury. The data point to CT-1 as a new promising hepatoprotective therapy and may provide a potential clinical strategy to improve the outcome of small-for-size liver grafts[73, 120].

Administration of CT-1 to rats or mice protects against ischemic/reperfusion liver injury and CT-1-deficient mice are exceedingly sensitive to this type of damage[107]. The data show that CT-1 is a natural defense of the liver against apoptosis and may have therapeutic potential[109].

Administration of CT-1 in animals with fulminant hepatic failure (FHF) had a survival rate of 80 %, which was significantly higher than that of nontreatment (28 %). In addition, improvement of liver histologic findings, shortening of activated clotting time, and decrease in serum levels of total bilirubin and alanine aminotransferase were detected with CT-1 treatment. Administration of CT-1 decreased apoptotic cells, increased Ki-67 cells in the liver tissues and increased expression of gp130 and up-regulation of cyclin D1 and hsp 90. In conclusion, cardiotrophin 1 may improve the outcome of FHF through its effects on antiapoptosis and cell repair[105].

CT-1 and Neural Tissue and Neuromuscular system diseases

CT-1 is neuroprotective in an in vitro model of cerebral ischemia[52, 96]. Cortical neurons synthesize and secrete CT-1, which activates the gp130-JAK-STAT pathway and is essential for the timed genesis of astrocytes in vitro. It was also demonstrated production of CT-1 in the postnatal and adult CNS, specifically by cell types comprising the blood-CSF barrier, and its accumulation in ventricular

Table 3. CT-1 and consequences with other diseases and organ systems,

Retina diseases	In rats with rapid photoreceptor degeneration there was a significant increase in phosphorylated STAT1 and -3 in the retina after CT-1 injection. These results indicate that CT-1 promotes photoreceptor survival and that Müller cells probably mediate this effect. Data also suggest that sustained delivery of the protein is essential for long-term rescue of photoreceptors[74].
Bone diseases	Mouse oncostatin M (OSM), LIF and CT-1 induce osteoclast differentiation and activation. Dexamethazone (DEX) synergizes with each in this activity, and OSM induces responses in osteoblasts that are not shown by LIF or CT-1. Collectively these data suggest an important role of these cytokines in osteoporosis caused by high levels of corticosteroid[33].
Lung diseases	CT-1 reduced the apoptosis induced both by serum deprivation and by Fas antibody/TNF-alpha treatment in adult human bronchial smooth muscle cells (HBSMC), with greater efficacy than other members of the IL-6 superfamily. The MAPK/ERK kinase inhibitor PD98059 reduced the effect of CT-1 (ref.[86]). Treatment with CT-1 in a chronic hypoxic pulmonary hypertension model protects the endothelial function of the pulmonary artery; decreases pulmonary arterial pressure; and attenuates right ventricular hypertrophy[72].
Cancer	Analysis of KB epidermoid cancer cell line culture supernatants after CT-1 treatment indicates that CT-1 stimulates their production of interleukin 6 (IL-6) in a time- and dose-dependent manner. This study suggests that at least in some pathological situations CT-1 might represent an immunomodulator regulating cytokine-induced gene products[17].
Blood cells	CT-1 administration increased the platelet counts by 70 %, with no change in mean platelet volume. Red blood cell counts were increased in the treated animals, and there was a concomitant increase in haemoglobin concentration[14]. CT-1 induces IL-6 mRNA and protein expression in monocytes in a time- and concentration-dependent manner. The underlying pathway is JAK2/STAT3, p38 and NFkappaB dependent[113].
Inflammation	CT-1 is a strong acute-phase mediator for hepatocytes in vitro and its activity is similar to LIF on hepatocytes, H35 cells, and HepG2 cells. Altogether, these results suggest that CT-1 could play an important role in the regulation of inflammatory responses[18].

ependyma. This finding has broad implications for CT-1 functioning apart from other leukemia inhibitory factor receptor ligands as a CSF-borne signal of brain homeostasis, one possibly involving regulation of the barrier itself, the ependyma or target cells in the surrounding parenchyma, including the subventricular zone[85].

CT-1 is expressed at high levels in embryonic limb bud and is secreted by differentiated myotubes. CT-1 may be important in normal motoneuron development and as a potential tool for slowing motoneuron degeneration in human diseases[12]. The treatment with adenovirus encoding CT-1 failed to protect facial nerve neurons after avulsion in adult rats[70]. CT-1 plays a key role in regeneration and hypertrophy in the skeletal muscle of rats[93].

Some familial ALS cases (FALS) have been linked to dominant mutations in the gene encoding Cu/Zn superoxide dismutase (SOD1). Intramuscular injection of an adenoviral vector encoding CT-1 in SOD1G93A newborn mice resulted in systemic delivery of CT-1, supplying motoneurons with a continuous source of the trophic factor. CT-1 delayed the onset of motor impairment. Axonal degeneration was slowed and skeletal muscle atrophy was largely reduced by CT-1 treatment. Thus, adenovirus-mediated gene transfer of neurotrophic factors might delay neurogenic muscular atrophy and progressive neuromuscular deficiency in ALS patients[56, 70]. Administration of an adenoviral CT-1 vector to newborn progressive motor neuropathy mice leads to sustained CT-1 expression in the injected muscles and bloodstream, prolonged survival of animals, and improved motor functions. CT-1-treated mice showed a significantly reduced degeneration of facial motoneuron cytons and phrenic nerve myelinated axons. The terminal innervation of skeletal muscle, grossly disturbed in untreated mice, was almost completely preserved in CT-1-treated mice[28]. Progressive motor neuropathy mice treated with a single injection/electroporation of a CT-1-encoding plasmid gain global weight, their mean lifespan is extended by 25 %, all their electromyographic parameters are improved and myelinated axons of their phrenic nerves are protected. Moreover, it was shown that re-injection/electroporation leads to improvements in this neuroprotection.Cytokines induce motoneuron survival through a PI 3-kinase activation requiring de novo protein synthesis dependent on Jak pathway[59]. Intra-muscular injection of adenoviral vector expressing CT-1, even at very low dose, improves median survival, delays motor defect of mutant mice with spinal muscular atrophy (SMA) and exerts protective effect against loss of proximal motor axons and aberrant cytoskeletal organization of motor synaptic terminals. In spite of the severity of SMA phenotype in mutant mice, CT-1 is able to slow down disease progression. Neuroprotection could be regarded as valuable therapeutic approach in SMA[71]. CT-1 deficiency causes increased motoneuron cell death in spinal cord and brainstem nuclei of mice during a period between embryonic day 14 and the first postnatal week. Interestingly, no further loss was detectable during the subsequent postnatal period, and nerve lesion in young adult CT-1 deficient mice did not result in significant additional loss of motoneurons, as had been previously observed in mice lacking both CNTF and LIF. CT-1 is the first bona fide muscle-derived neurotrophic factor to be identified that is required for the survival of subgroups of developing motoneurons[46]. It was concluded that CT-1 exerts myotrophic effects as well as neurotrophic effects in a mouse model of spontaneous moto neuron disease (MND), a finding that has potential therapeutic implications for human MND[51].

Summary of consequences between CT-1 and some additive organ systems and diseases are displayed below (Table 3).

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