Deadly liaisons: fatal attraction between CCN matricellular proteins and the tumor necrosis factor family of cytokines

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Abstract Recent studies have revealed an unexpected synergism between two seemingly unrelated protein families: CCN matricellular proteins and the tumor necrosis factor (TNF) family of cytokines. CCN proteins are dynamically expressed at sites of injury repair and inflammation, where TNF cytokines are also expressed. Although TNFα is an apoptotic inducer in some cancer cells, it activates NFκB to promote survival and proliferation in normal cells, and its cytotoxicity requires inhibition of de novo protein synthesis or NFκB signaling. The presence of CCN1, CCN2, or CCN3 overrides this requirement and unmasks the apoptotic potential of TNFα, thus converting TNFα from a proliferation-promoting protein into an apoptotic inducer. These CCN proteins also enhance the cytotoxicity of other TNF cytokines, including LTα, FasL, and TRAIL. Mechanistically, CCNs function through integrin α6β1 and the heparan sulfate proteoglycan (HSPG) syndecan-4 to induce reactive oxygen species (ROS) accumulation, which is essential for apoptotic synergism. Mutant CCN1 proteins defective for binding α6β1-HSPGs are unable to induce ROS or apoptotic synergism with TNF cytokines. Further, knockin mice that express an α6β1-HSPG-binding defective CCN1 are blunted in TNFα- and Fas-mediated apoptosis, indicating that CCN1 is a physiologic regulator of these processes. These findings implicate CCN proteins as contextual regulators of the inflammatory response by dictating or enhancing the cytotoxicity of TNFα and related cytokines.

Keywords Inflammation · Apoptosis · TNF · FasL · TRAIL · CYR61 · CTGF · NOV

Introduction

Apoptosis is an evolutionarily conserved process in multicellular organisms for eliminating unwanted or damaged cells, and is critical for normal development and tissue homeostasis. Environmental factors, such as UV irradiation or oxidative stress, can cause or increase susceptibility to apoptosis. A number of endogenously produced proteins, notably members of the tumor necrosis factor (TNF) family of cytokines including TNFα, lymphotoxin-α (LTα), Fas ligand (FasL), and TNF-related apoptosis-inducing ligand (TRAIL), can induce apoptosis by binding to specific receptors on the surface of target cells. The ensuing signaling events, characterized by the activation of the caspase family of intracellular proteinases, lead to cell shrinkage and DNA fragmentation. The resulting cellular debris is engulfed and removed by macrophages and other surrounding cells.

The extracellular matrix (ECM) has long been recognized as a critical survival factor. Cell adhesion to ECM proteins such as fibronectin through integrin receptors activates cytoprotective signaling pathways involving PI3K, JNK, and ERK to suppress apoptosis (Almeida et al. 2000). When deprived of proper interaction with the ECM or if integrins are unligated or improperly ligated, normal cells undergo a form of apoptosis called anoikis (Cheresh and Stupack 2008; Chiarugi and Giannoni 2008). Contrary to the prevailing view that the ECM serves a pro-survival role, recent studies have revealed that certain ECM molecules can promote or induce apoptosis (Marastoni et al. 2008). For example, the CCN family of proteins can
promote apoptosis through integrin-dependent activation of p53 even as they support cell adhesion and induce adhesive signaling (Todorovic et al. 2005), whereas EMILIN2 can induce apoptosis by binding to the death receptors DR-4 and DR-5 (Mongiat et al. 2007). Surprisingly, CCN proteins can also enable or promote the cytotoxicity of the TNF family cytokines both in vitro and in vivo, thus altering the matrix microenvironment to dictate or support TNF cytokine-dependent cell death (Fig. 1). This review focuses on the novel signaling crosstalk that underpins the unexpected synergism between these two seemingly unrelated protein families.

Apoptotic synergism between members of the CCN and TNF families

The CCN family is comprised of six structurally conserved, ECM-associated signaling proteins in vertebrates (Leask and Abraham 2006; Holbourn et al. 2008; Chen and Lau 2009). The first three members described, Cyr61 (cysteine rich 61, CCN1), connective tissue growth factor (CTGF, CCN2), and nephroblastoma overexpressed (Nov, CCN3), provided the acronym for the CCN family. CCNs regulate diverse aspects of cell behavior including cell adhesion, migration, proliferation, survival, and differentiation without being integral structural components of the matrix, and as such they fit the characteristics of “matricellular” proteins (Bornstein 1995; Lau and Lam 1999). Like many ECM proteins, they function through direct interaction with integrin receptors and cell surface heparan sulfate proteoglyans (HSPGs) to mediate many of their activities (Kireeva et al. 1998; Chen et al. 2000).

The TNF superfamily includes at least 19 cytokines that play critical roles in regulating the development and function of the immune system (Locksley et al. 2001; Aggarwal 2003). A subset of this family, such as TNFα, LTα, FasL, and TRAIL, can also induce cell death. TNF cytokine-dependent cell death may play important roles in the removal of damaged or potentially cancerous cells as part of immune surveillance, but can also contribute to the etiology of a variety of diseases if it occurs excessively. TNFα was initially found to induce necrotic and apoptotic death in certain cancer cells; however, subsequent studies showed that TNFα alone promotes survival of normal cells in culture and its cytotoxicity is only revealed when de novo protein synthesis or NFκB signaling is blocked (Varfolomeev and Ashkenazi 2004; Muppidi et al. 2004). TNFα activates the transcription factor NFκB, which induces the expression of a large number of proteins critical for cell survival and inflammation. Since TNFα can activate both survival and apoptotic signaling, its cytotoxicity is highly contextual and dependent on the presence of sensitizing contributors such as viral infection or IFN-γ that perturbs NFκB signaling or protein synthesis (Varfolomeev and Ashkenazi 2004; Muppidi et al. 2004). LTα binds the same receptors as TNFα and is thought to act similarly. By contrast, FasL and TRAIL are weak inducers of NFκB and can induce cell death on their own; however, their cytotoxicity is also regulated by other environmental factors.

In adults, CCNs are highly expressed at sites of tissue damage and inflammation where TNF family cytokines are also expressed in many instances, providing the opportunity for CCNs and TNF cytokines to interact. Recently we showed that CCN1 and CCN2, either in a soluble form or as adhesion substrates, enable TNFα to induce apoptosis without perturbation of protein synthesis or NFκB signaling, and enhance the cytotoxic effects of FasL and TRAIL (Chen et al. 2007; Juric et al. 2009; Franzen et al. 2009). Indeed, the interactions between the CCN and TNF families extend even further: CCN1, CCN2, and CCN3, can each unmask the cytotoxicity of TNFα and LTα, and promote the apoptotic activity of FasL and TRAIL in normal human fibroblasts, resulting in rapid apoptosis within 4–6 h (Fig. 2). Although CCNs do not trigger cell death on their own under these conditions, they induced apoptosis in ~25% of cells in combination with TNFα or LTα, and enhanced the apoptotic efficacy of FasL and TRAIL by at least 2-fold (Fig. 2). These observations are remarkable, since TNFα normally promotes the proliferation of fibroblasts by inducing the expression of PDGF and is not

![Fig. 1](image-url)
cytotoxic (Battegay et al. 1995). Thus, the presence of CCNs turns TNFα from being a proliferation-enhancing agent into a cytotoxic factor. These activities appear unique to members of the CCN family and were not found in other ECM proteins tested, such as collagen, fibronectin, laminin, and vitronectin.

NFκB suppresses the cytotoxicity of TNFα

When TNFα engages its cell surface receptor TNFR1, the death domain in the receptor cytoplasmic tail recruits the adaptor protein TRADD, which further recruits RIP and TRAF2 that participate in the activation of NFκB and JNK (Fig. 3). The RIP, TRAF2, and TRADD complex (complex I) subsequently dissociates from the receptor and recruits FADD and procaspase-8/-10 into a secondary complex (complex II) in which activation of procaspase-8/-10 occurs (Muppidi et al. 2004; Bertazza and Mocellin 2008). Whereas caspases-8/-10 can directly activate caspase-3 by proteolysis to trigger apoptosis, in some cell types caspase-8 cleaves and activates the BH3-only protein Bid, leading to cytochrome c release from the mitochondria and amplification of the apoptotic signal. Cytoplasmic cytochrome c complexes with Apaf-1 and activates caspase-9, which further activates caspase-3 to trigger apoptosis.

In normal cells, the pro-survival protein c-FLIP competes with procaspases-8/-10 for binding to the RIP/TRADD/TRAF2/FADD complex, thus preventing caspase activation. TNFα-activated NFκB induces the transcription and synthesis of c-FLIP, adding to the existing cellular pool of c-FLIP and creating a further obstacle to caspase activation. The function of c-FLIP is opposed by the stress-induced kinase JNK, which promotes apoptosis by phosphorylating the ubiquitin ligase ITCH and thereby targeting c-FLIP for degradation (Chang et al. 2006). If JNK activation is robust and prolonged, c-FLIP is obliterated and TNFα-induced apoptosis can occur. However, under normal conditions TNFα-activated JNK is rapidly inactivated by phosphatases. Reactive oxygen species (ROS), which are generated as microbicides in phagocytic cells, or as second messengers mediating diverse cellular functions in non-phagocytic cells, are important regulators of JNK because they can inactivate phosphatases by oxidation of the critical cysteine residue in the enzyme active centers (Meng et al. 2002). Thus, a high level of
cellular ROS can inactivate phosphatases and allow TNFα-induced JNK activation to remain sustained, thereby leading to c-FLIP degradation and apoptosis (Kamata et al. 2005). Although TNFα itself induces ROS production, TNFα-induced ROS are quickly downregulated by NFκB, which activates the synthesis of anti-oxidant proteins such as Mn-superoxide dismutase and ferritin heavy chain (Pham et al. 2004). In addition, NFκB can induce the expression of phosphatases to restrain JNK activation. Therefore, NFκB counteracts the TNFα-induced apoptotic pathway by inducing the synthesis of c-FLIP, phosphatases, and antioxidant proteins, all of which conspire to block TNFα-induced apoptosis.

**CCNs enables TNFα cytotoxicity and promotes FasL activity through ROS**

Although inhibition of de novo protein synthesis or NFκB signaling is the most common way to enable TNFα induction of apoptosis in normal cells, CCNs do not perturb either process. In addition, CCN1 and TNFα induces ~2-fold more apoptosis and with a much faster kinetics (4–6 h vs. 24 h) compared to apoptosis induction by cycloheximide and TNFα, further suggesting that CCN1 works through a distinct mechanism (Chen et al. 2007). Indeed, CCNs act through inducing the accumulation of a high level of ROS to override the anti-apoptotic effects of NFκB, thus unmasking the cytotoxicity of TNFα (Fig. 4). Both CCN1 and CCN2 induce ROS production in fibroblasts, and neutralization of ROS with chemical scavengers or inhibiting cellular mechanism of ROS production annihilates their apoptotic synergism with TNFα and FasL (Chen et al. 2007; Juric et al. 2009). TNFα alone induces a transient JNK activation and a low level of ROS that is quickly dampened by NFκB-induced anti-oxidant proteins. Despite NFκB actions, the combination of CCN1 and TNFα induces a sufficient amount of ROS to trigger a robust and biphasic activation of JNK (Chen et al. 2007). Upon CCN1/TNFα treatment, JNK activation occurs within 15 min, but transiently declines between 1 and 3 h after stimulation, most likely due to NFκB-induced synthesis of new phosphatases. Eventually CCN1-induced ROS may inhibit the newly synthesized phosphatases and a second phase of JNK activation occurs between 4 and 6 h after stimulation, concomitant with cell death. This second phase of JNK activation, which is not seen in TNFα stimulation alone, is essential for CCN1/TNFα-induced apoptosis.

In CCN1/FasL synergism, CCN1 induces ROS to hyperactivate p38 MAPK, leading to the activation and mitochondrial localization of Bax and consequent cytochrome c release (Juric et al. 2009). Other reports also show that p38 can phosphorylate and inhibit the pro-survival activity of members of the Bel-family, thereby promoting Bax/Bak activation and mitochondrial cytochrome c release (Tocria et al. 2001; Gomez-Lazaro et al. 2007). However, ROS does not seem to play an important role in CCN1 synergism with TRAIL in PC-3 prostate cancer cells, suggesting cell-type specific differences in the mechanism of apoptotic synergism (Franzen et al. 2009). Interestingly, CCN1 action is a double edge sword in prostate carcinoma cells, since it promotes the proliferation of prostate cells but also enhances the cytotoxicity of TRAIL. Thus, cancer cells may overexpress CCN proteins to promote their proliferation, although this also puts them at risk of higher susceptibility to TRAIL-mediated immune surveillance.

**Mechanisms of ROS induction by CCN1**

Integrin-mediated cell adhesion to ECM proteins generates ROS, which is required for the adhesion process (Chiarugi et al. 2003). Integrin signaling is known to activate small GTPases such as RAC and RHO, leading to disassembly and repolymerization of F-actin, formation of lamellipodia, and clustering of ligand-bound integrins into focal complexes. RAC can also regulate ROS generation through multiple mechanisms, including 5-lipoxygenase (LOX) (Chiarugi et al. 2003), specific isoforms of NADPH oxidases (NOX) (Chiarugi et al. 2003), and the mitochondria (Werner and Werb 2002)(Fig. 4). Whereas LOX...
catalyzes the metabolism of arachidonic acid to leukotrienes, NOX generates free superoxide from molecular oxygen and is the predominant source of ROS in phagocytic cells. Integrin-mediated fibroblast adhesion to CCN1 and CCN2 activates RAC1 (Chen et al. 2001), which induces ROS generation through 5-LOX and mitochondria for apoptotic synergism with TNFα (Chen et al. 2007). CCN1 interaction with integrins αvβ5, αvβ1, and the HSPG syndecan-4 is required for this process, and this requirement of multiple receptors may help specify the target cells for elimination. Although TNFα itself induces ROS via NOX-dependent mechanisms to mediate apoptosis and necrosis (Chen et al. 2007; Kim et al. 2007; Yazdanpanah et al. 2009), inhibition of NOX has no effect on CCN1/TNFα synergism, showing a remarkable specificity of ROS in these distinct pathways.

A recent study shows that CCN1 can activate neutral sphingomyelinase 1 (nSMase1) (Juric et al. 2009), which generates the lipid second messenger ceramide that can increase ROS through several mechanisms (Won and Singh 2006). In CCN1/FasL synergism, the activation of nSMase1 plays a critical role in the generation of ROS that triggers the hyperactivation of p38, leading to enhanced Bax activation and cytochrome c release. The discovery that matrix proteins can activate nSMase1 is without precedent, and the mechanism of nSMase1 activation through integrin signaling is currently unknown.

### In vivo evidence of the synergism

Since Ccn1- and Ccn2-null mice are embryonic and perinatal lethal, respectively, they cannot be used to address the roles of CCNs in TNFα or Fas-mediated apoptosis in vivo. To circumvent this problem, knockin mice were created in which the Ccn1 genomic locus was replaced by an allele encoding DM, a CCN1 mutant that is disrupted in two αvβ1-HSPG binding sites located in the carboxy-terminal domain (Chen et al. 2000, 2007). The resultant CCN1-DM protein is still active in promoting αv integrin-mediated cellular activities (Leu et al. 2004), but is unable to induce ROS accumulation or synergize with TNFα or FasL to promote fibroblast apoptosis (Chen et al. 2007; Jurie et al. 2009). Unlike Ccn1-null mice, Ccn1ΔΔm/dm mice are viable, fertile, and show no obvious morphological or behavioral defects. When injected subcutaneously with a small bolus of soluble TNFα to induce dermal apoptosis, these mutant mice showed >60% reduction in apoptosis in dermal cells compared to wild-type mice, consistent with CCN1/TNFα synergism in vivo (Chen et al. 2007).

To study TNF cytokine-mediated cytotoxicity in vivo, Ccn1ΔΔm/dm mice were tested in three different models of hepatotoxin-induced apoptosis: intravenous injection of an agonistic monoclonal antibody that activates Fas (clone Jo2), and intragastric administration of alcohol. ConA induces robust TNFα synthesis in macrophages and T cells and leads to massive TNFα-dependent hepatocyte apoptosis, which is completely abrogated by neutralizing antibodies against TNFα or by genetic ablation of TNFR1 and TNFR2 (Trautwein et al. 1998; Wolf et al. 2001). To examine Fas-mediated apoptosis, the monoclonal antibody Jo2 recognizes and activates the Fas receptor to induce Fas-mediated apoptosis, a process that is annihilated by genetic disruption of Fas, demonstrating the specificity for Fas (Ogasawara et al. 1993). In addition, ethanol gavage in mice mimics binge drinking and results in FasL-induced hepatocyte apoptosis that is ablated by neutralizing antibodies against FasL (Zhou et al. 2001). In all three experimental models, Ccn1ΔΔm/dm mice consistently show >60% reduction in hepatocyte apoptosis compared to wild-type mice (Fig. 5) (Juric et al. 2009; Chen et al. 2007). These results show that CCN1 is a physiological regulator of TNFα and Fas-mediated apoptosis in vivo, and suggest an important role for CCN1 in the pathogenesis of toxin-induced hepatitis. However, these findings do not exclude the participation of other factors such as IFNγ, which may regulate TNF cytokine cytotoxicity in certain contexts.

![In vivo evidence of the synergism](image)

Fig. 5 CCN1 is critical for TNFα and Fas-mediated apoptosis in vivo. Ccn1ΔΔm/dm knockin mice express the CCN1 mutant DM, which is disrupted in the binding sites for αvβ1 and HSPGs and is therefore unable to induce ROS or apoptosis. TNFα-induced apoptosis was tested by either direct subcutaneous injection of TNFα, or by treatment with ConA, which induces TNFα production from macrophages (Chen et al. 2007). Fas-mediated apoptosis was tested by tail-vein injection of the agonistic mAb, Jo2, or by a gavage of ethanol. In each scenario, apoptosis is reduced by 60–70% in Ccn1ΔΔm/dm mice compared to wild-type mice, indicating that CCN1 is critical for optimal TNFα and Fas-mediated apoptosis in vivo.
Future questions

The results summarized above indicate that CCN matricellular proteins are contextual regulators of several TNF family cytokines, dictating or promoting their cytotoxicity. However, many other questions still remain. Since cell adhesion to other ECM proteins also generates ROS, what might be the underlying mechanism that sets CCNs apart in being able to synergize with TNFs? Do the remaining members of the CCN and TNF families interact, and do CCNs regulate TNF family cytokine functions other than apoptosis? Beyond fibroblasts and hepatocytes, which cell types are susceptible to CCN/TNF synergism?

Since CCNs and TNFα are coexpressed at sites of inflammation, it is tempting to speculate that CCNs may help to terminate the inflammatory responses initiated by TNFα by unmasking its apoptotic function. Inasmuch as chronic inflammation and elevated TNFα levels contribute to the morbidity of many diseases, CCN/TNF interaction may play an important role in the loss of functional cells during disease progression. For example, in acute and chronic diseases of the liver, such as hepatitis, fibrosis, and fulminant liver failure caused by viral infection, alcohol abuse, and hepatotoxin exposure, elevated levels of TNFα are observed and in some cases TNFα-dependent apoptosis correlate with disease severity (Muto et al. 1988; Czaja et al. 1989; Bird et al. 1990; Gonzalez-Amaro et al. 1994; Blazka et al. 1995; Shibata et al. 2008). Beyond hepatic pathology, other contexts in which CCN/TNF-mediated apoptosis may play a role include placental inflammation and cardiomyopathy, since CCN expression and marked TNFα-dependent apoptosis occur concurrently (Haider and Knofler 2009; Yaoita and Maruyama 2008). The possibility that CCN/TNF synergism may play important roles in the pathogenesis of various diseases mentioned above is intriguing and clearly merits further investigation.

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Apoptotic synergism between CCN proteins and TNF cytokines

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