New insights into the biological role of COMMD1
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CHAPTER 2

Tuning NF-κB: A touch of COMMD proteins

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ABSTRACT

NF-κB is an important regulator of immunity and inflammation, and its activation pathway has been studied extensively. The mechanisms that downregulate the activity of NF-κB have also received a lot of attention, particularly since its activity needs to be terminated to prevent chronic inflammation and subsequent tissue damage. The COMMD family has been identified as a new group of proteins involved in NF-κB termination. All ten COMMD members share the structurally conserved carboxy-terminal motif, the COMM domain, and are ubiquitously expressed. They seem to play distinct and non-redundant roles in various physiological processes, including NF-κB signaling. In this review, we describe the mechanisms and proteins involved in the termination of canonical NF-κB signaling, with a specific focus on the role of the COMMD family in the down-modulation of NF-κB.
INTRODUCTION

The nuclear factor-κB (NF-κB) family of transcription factors regulates the expression of a wide array of genes involved in various physiological processes, including immunity and inflammation. The central role of NF-κB in these processes is to recruit and activate various immune cells by inducing transcription of proinflammatory mediators like cytokines, chemokines and adhesion molecules. This process aims to protect the host efficiently against different kind of pathogens and injuries. However, it is essential that in the end NF-κB activity is downregulated in order to prevent chronic inflammation. Uncontrolled inflammation can be accompanied by tissue damage (reviewed in [1]) and can have a critical role in the development and pathogenesis of numerous diseases, like inflammatory bowel disease, atherosclerosis, diabetes and cancer [2-7]. Therefore, NF-κB activity during inflammatory responses needs to be tightly spatiotemporally regulated. This review discusses several pathways down-modulating NF-κB activity, and pays special attention to the role of the COMMD family of proteins in NF-κB signaling.

The NF-κB family comprises five members: RELA (p65), RELB, c-REL, p50/p105 (NF-κB1), and p52/p100 (NF-κB2), which all share the amino-terminal REL homology domain (RHD). The RHD is essential for various events, such as NF-κB dimerization, interaction with inhibitors of κB (IκB), nuclear translocation and binding to DNA. RELA, c-REL and RELB proteins also have a transcriptional activation domain (TAD) at the carboxy-terminus, which is important for the transcription of NF-κB target genes. The TAD is absent in the NF-κB subunits p50 and p52, therefore they can function as transcriptional repressors (reviewed in [8]). Whether NF-κB acts as a transcriptional activator or repressor depends on the dimer combination formed by the NF-κB members. NF-κB dimers which contain at least one member with a TAD activate transcription through displacement of repressors, such as the histone deacetylases 1 and 2 (HDAC1 and HDAC2), and recruitment of co-activators, i.e. HDAC3 [9, 10] and the histone acetylases, CBP/p300 [11-13]. In contrast, p50 and p52 homodimers or p50/p52 heterodimers, which both bind to κB-sites, have been shown to have a transcriptionally repressive function. This function is manifested by recruiting transcriptional repressors, such as HDAC1 [14, 15].

The way that NF-κB is activated can be divided into various signaling pathways, including the canonical (or classical) and the non-canonical (or alternative) pathway. Which of the signaling events occurs depends on the type of stimuli. The canonical pathway is activated by a wide range of stimuli, such as the proinflammatory cytokines, tumor necrosis factor (TNF), interleukin-1 (IL-1) and the bacterial endotoxin, lipopolysaccharide (LPS). These stimuli activate the NF-κB dimer RELA/p50 through the receptors: TNF receptor (TNFR), interleukin 1 receptor (IL-1R) and the toll-like receptor 4 (TLR4), respectively. The non-canonical pathway can be activated by lymphotoxin beta, B cell activating factor, or CD40 ligand. This activation induces the processing of p100 that results in RELB/p52 mediated transcription. Since we will focus mainly on the regulation of the canonical
pathway here, we recommend readers to other reviews for further information on the non-canonical and other pathways in NF-κB activation (for example [16-18]).

In the canonical NF-κB pathway, the NF-κB dimer RelA/p50 is kept in the cytosol in an inactive state by the IκB proteins. These proteins retain RELA/p50 dimers in the cytosol by masking their nuclear localization signal (NLS) (Fig. 1). This prevents translocation of RELA/p50 to the nucleus. However, it has been indicated that IκB proteins, namely IκBα and IκBε, also have the ability to shuttle NF-κB from the nucleus back to the cytoplasm. This is regulated by the nuclear export signal (NES) within these proteins, which is absent in the other IκB proteins. Upon phosphorylation of the IκB proteins by the IκB kinase (IKK) complex, IκB proteins are ubiquitinated and subsequently degraded by the proteasomes (Fig. 1). This results in nuclear translocation of RELA/p50. Dimeric combinations of RelA subunit (NF-κB) bind to the DNA regions upstream of specific genes to alter their transcription.

The IKK complex consists of two catalytic subunits with kinase activity (IKKα/IKK1 and IKKβ/IKK2) and a regulatory subunit (IKKγ, also known as NEMO) [19]. IKK activation is mediated by different protein complexes downstream of various receptors that are responsible for the initial NF-κB activation (reviewed in [20]). This pathway has been studied extensively since NF-κB was first identified in 1986 [21]. However, there is still relatively little known about the mechanisms that terminate its transcriptional activity or the signaling events that are essential to resolve inflammation and prevent autoimmune disease.

DOWN-MODULATORS OF NF-κB

To this day, only a few proteins have been shown to negatively regulate NF-κB signaling [22, 23]. Among them are the IκB proteins (IκBα, IκBβ, and IκBε). Upon NF-κB activation, the expression of both IκBα and IκBε is induced as a negative feedback loop mechanism. Although the expression of IκBε is markedly delayed compared to IκBα, both newly synthesized IκB proteins sequester NF-κB in the cytosol in order to hamper the activity of NF-κB [24] (Fig. 1). On the contrary, it has been shown that hypophosphorylated IκBβ can form a DNA-bound protein complex with RELA, which leads to prolonged expression of NF-κB target genes [25]. Thus IκBβ can regulate NF-κB either negatively or positively. In addition to the IκB proteins, the protein A20/TNFAIP3 similarly serves as a negative feedback loop, with its expression also driven by NF-κB (Fig. 1). The deubiquitinating (DUB) enzymatic activity of A20 is responsible for removal of the K63-linked polyubiquitin chains from the receptor-interacting protein 1 (RIP1). At the same time, the E3 ubiquitin ligase domain of A20 promotes K48-ubiquitin mediated RIP1 protein degradation [26]. In addition to RIP1, A20 also deubiquitinates other IKK regulators, such as NEMO and TRAF6. This event eventually results in downregulation of the canonical NF-κB signaling cascades. The importance of this negative feedback loop mechanism is illustrated in several murine models. Haploinsufficiency for A20 in apolipoprotein E-deficient mice leads to increased atherosclerotic lesion size and conditional depletion of A20 in certain murine
NF-κB activity in the nucleus, either interfering with the binding of NF-κB to the DNA or leading to NF-κB ubiquitination and proteasomal degradation.

cell types, such as B-cells, dendritic cells (DCs), intestinal epithelial cells or macrophages and granulocytes, leads to hypersensitivity to various inflammatory diseases, such as colitis and nephritis [27, 28]. Furthermore, complete deficiency of A20 results in early death due to uncontrolled inflammation. Of note, human single nucleotide polymorphisms (SNPs) within the A20 gene have been associated with susceptibility to several diseases like rheumatoid arthritis, psoriasis, celiac disease, Crohn’s disease, systemic sclerosis, and type 1 diabetes. Moreover, A20 insufficiency has been shown to play an important role in human B cell lymphoma [27].

Another protein playing a role in dampening the activity of NF-κB is the DUB protease, cylindromatosis (CYLD) [29-31]. CYLD deubiquitinates NEMO and several other upstream proteins like RIP1, TAK1, TRAF2, 6, and 7 [29]. The K63-linked ubiquitin chains removed by CYLD are essential for down-modulation of IKK activity (Fig. 1). Cyld-deficient mice are prone to inflammation and tumor formation in various experimental mouse models [32,33]. In humans, mutations in CYLD are associated with the development of cylindromas (tumors of the skin) [34-36]. In contrast, Cyld-deficient mice do not develop skin tumors.
spontaneously, but are sensitive to chemically induced skin tumors. Furthermore, reduced expression of CYLD has been observed in colon and liver cancers in humans [37]. Together, these experimental murine models and human genetic studies underline the importance of NF-κB down-modulation in preventing uncontrolled inflammation and the development of diseases associated with inflammation.

All the events described above control NF-κB activity by acting upstream of NF-κB. However, little is known about the mechanisms through which NF-κB activity is terminated within the nucleus. In addition to IκBα, which relocates active RELA from nucleus back to the cytosol for proteasomal degradation [38], other proteins that directly inhibit NF-κB at the DNA level have been identified. These include PDZ and LIM domain containing protein 2 (PDLIM2), protein inhibitor of activated STAT (PIAS), and COMMD1 (Fig. 1). PDLIM2 is an ubiquitin E3 ligase [39], which directs RELA from the nucleus into subnuclear domains, also known as promyelocytic leukemia protein (PML) nuclear bodies [40]. Upon polyubiquitination by PDLIM2, RELA is degraded by the proteasomes within the PML nuclear bodies. Pdlim2-deficient mice are more sensitive to LPS-induced sepsis, illustrating the importance of PDLIM2 in restraining inflammation [39].

PIAS1 interferes with the binding of NF-κB to the κB-sites of NF-κB target genes. In a similar fashion to Pdlim2 null mice, loss of Pias1 in mice results in hypersensitivity to endotoxic shock [41]. The latter has also been observed in Pias4-deficient mice, indicating that Pias1 and Pias4 are not redundant in this specific pathway [42]. In addition to the previously discussed proteins, COMMD1, a member of the COMMD family of proteins, has been identified as playing a role in terminating NF-κB at the level of DNA. Similar to PIAS1 and PIAS4, COMMD1 inhibits the expression of a specific subset of NF-κB target genes [43]. The mechanism by which COMMD1 down-modulates NF-κB will be described in the following paragraphs.

THE COMMD PROTEIN FAMILY

COMMDS – A FAMILY OF NF-κB REGULATORS

Using a positional cloning strategy, COMMD1 was first identified to be mutated in Bedlington terriers suffering from copper toxicosis [44]. Copper toxicosis is characterized by copper accumulation in the liver until reaching toxic levels resulting in pathological changes (the role of COMMD1 in copper homeostasis is discussed in paragraph 3.5 of this manuscript). Soon after this discovery, E. Burstein and colleagues demonstrated that COMMD1 belongs to a new family of proteins, called the Copper Metabolism gene MURR1 Domain-containing (COMMD) family [45]. This family consists of ten members and is highly conserved in various multicellular organisms and in some protozoa. The COMMD proteins have a structurally conserved carboxyl-terminal Copper Metabolism gene MURR1 (COMM) domain [45] (Fig. 2). This domain serves as a platform for COMMD interactions with each other and with their interacting partners. The amino-terminal region...
is unique in each COMMD protein, but is almost absent in COMMD6, as COMMD6 primarily encodes the COMM domain (Fig. 2). All COMMD proteins, including COMMD1, were shown to interact with COMMD1 [45, 46]. The COMMD proteins are ubiquitously expressed, but the level of mRNA expression of each COMMD varies within and between different tissues [44, 45]. As an example, oligonucleotide microarray data demonstrated that COMMD1 is highly expressed in the testis and heart, but much less so in skin [45]. Nevertheless, there seems to be no direct correlation between mRNA and protein expression, since the highest protein levels of Commd1 in mice are seen in kidney, colon, spleen and liver [47]. Of note, no catalytic activity has been assigned to the COMMD proteins.

Although in recent years more insight into the function of COMMD1 has been obtained, very little is known about the function of the other COMMD proteins. Nonetheless, according to Burstein et al. [45], all COMMD proteins are able to interact with different subunits of NF-κB. Additionally, based on a luciferase κB-reporter assay, each COMMD member, when overexpressed, inhibits TNF-induced NF-κB activity [45, 46]. Of note, only COMMD1 is able to interact with all five subunits of NF-κB, whereas the other COMMDs show a selective interaction pattern with NF-κB subunits [45]. Moreover, only an association between COMMD1 and IκBα has been identified so far [46, 48]. It is therefore likely that the mechanism by which each COMMD protein regulates NF-κB is distinct.
Despite the fact that all ten COMMD proteins interact with NF-κB, so far a detailed mechanism has only been described for COMMD1: it inhibits NF-κB by promoting the ubiquitination and subsequent proteasomal degradation of RELA bound to chromatin [43, 45] (Fig. 3). Depletion of COMMD1 results in prolonged nuclear RELA levels upon NF-κB activation, which coincides with increased and sustained expression of a specific group of NF-κB target genes. COMMD1 also downregulates the levels of RELB, p105 and p100. As shown initially for COMMD1 knockdown, the level of polyubiquitinated RELA was also reduced in cells insufficient for either COMMD6, 9 or 10 [43]. These data indicate that other COMMD proteins also mediate NF-κB activity by regulating the turnover of RELA, but more studies are needed to confirm this.

**Figure 3. Schematic overview of COMMD1 action in p65 (RELA) degradation and functional regulation of COMMD1.** COMMD1, a protein of ~ 21kDa enters the nucleus possibly by passive diffusion through the nuclear pores. It associates with ubiquitin E3 ligase complex ECSSOCS1. The interaction of COMMD1-ECSSOCS1 complex with RELA is promoted by phosphorylation of RELA on Ser468 residue. COMMD1 facilitates the interaction between SOCS1 (present in ECSSOCS1 complex) and RELA, which results in ubiquitination and subsequent proteasomal degradation of RELA. ARF promotes poly-K63-linked ubiquitination of COMMD1, which results in increased nuclear COMMD1 levels. COMMD1 can be actively transported out of the nucleus through the CRM1 receptor, utilizing two nuclear export sequences (NES) within its COMM domain. In the cytosol XIAP and HSCARG proteins play a role in COMMD1 K48-linked poly-ubiquitination. This modification leads to degradation of COMMD1 by the proteasomes. sCLU might also affect the level of ubiquitinated COMMD1, as its expression is inversely correlated with COMMD1 levels.
COMMD1 interacts with a multimeric E3 ubiquitin ligase complex of proteins, the ECS^SOCS1. This complex contains Elongins B and C, Cullin 2 and SOCS1 (Fig. 3). Within the ECS^SOCS1 complex, COMMD1 acts as a hub to facilitate the interaction between RELA and SOCS1, which results in increased polyubiquitination of RELA [43]. The physical association of COMMD1 and RELA depends on the phosphorylation of RelA at serine residue 468 (Ser468). Substitution of Ser468 with an alanine impedes this interaction and almost completely prevents COMMD1-mediated RELA ubiquitination and proteasomal degradation. Upon NF-κB activation, RELA S468A substitution results in prolonged binding of RELA to a selective set of NF-κB target genes [49-51]. Interestingly, after removal of RELA from the promoter site, COMMD1 was detected at the same promoter site [49]. These results suggest that after NF-κB termination, COMMD1 occupies the promoter sites of a specific subset of genes. This indicates that COMMD1 may also reduce the expression of NF-κB target genes by this additional mechanism. The fact that COMMD1 does not contain a DNA-binding motif suggests that it is in a complex with other proteins that occupy these specific promoter sites. However, the composition of this possible protein complex still has to be identified.

The importance of Ser468-phosphorylated RELA in NF-κB termination was confirmed by Mao et al. [52]. They showed that this specific post-translational event is important for the interaction of RELA with the histone acetyltransferase GCN5. In complex with COMMD1, GCN5 facilitates the ubiquitin-dependent proteasomal degradation of RELA. Although Mao et al. showed that IKKa and IKKβ are important for this phosphorylation-dependent regulation, Geng et al. indicated that it is particularly IKKe that regulates the phospho-S468 mediated RELA degradation [49, 52]. Of note, an interaction between COMMD10 and GCN5 has also been observed, but the biological relevance of this association is not yet understood.

**FUNCTIONAL REGULATION OF COMMD1**

Although COMMD1 is predominantly localized in the cytosol, low levels have also been observed in the nucleus [53-58]. Since it is a relatively small protein (21 kDa) and does not contain a nuclear localization signal (NLS), it is likely that COMMD1 enters the nucleus by diffusion through the nuclear pores. However, its transport from the nucleus back to the cytosol seems to be tightly regulated. COMMD1 has two nuclear export signals (NES) (Fig. 2) [55], which are recognized by CRM1 (Exportin 1), a nuclear export receptor present predominantly at the nuclear membrane (Fig. 3). Mutation of the NES or CRM1 inhibition leads to an increase in nuclear COMMD1. COMMD1 NES mutants augment the inhibitory function of COMMD1 on NF-κB. A similar role for NES to regulate the nuclear levels of COMMD1 and hereby its inhibitory effect during hypoxia was demonstrated [55]. NES mutations in COMMD1 reduce hypoxia-driven export of nuclear COMMD1 and coincide with greater inhibition of COMMD1 on hypoxia-inducible factor-1 (HIF-1)
activity [55]. The hydrophobic residues forming the NES (NES consensus sequence of HX$_{2-3}$HX$_{2-3}$HX$_{1-2}$H) are conserved among the COMMD proteins (Fig. 2) [55], but the role of these residues in nuclear localization of the COMMD proteins needs to be investigated.

Cytosolic COMMD1 can be polyubiquitinated by either X-linked inhibitor of apoptosis (XIAP) [53] or redox sensor protein HSCARG [58]. Both XIAP and HSCARG add K48-polyubiquitin chains to COMMD1, which direct COMMD1 for proteasomal degradation (Fig. 3). This mechanism likely controls COMMD1 levels and thereby its function on NF-κB. However, at the moment, only a role for XIAP in copper metabolism and COMMD1 regulation has been proposed [53, 61]. Intracellular copper enhances the degradation of XIAP and sensitizes cells to apoptosis [61]. Since COMMD1 was initially identified as a novel modulator of hepatic copper homeostasis, these results might accentuate the link between XIAP and COMMD1 in this specific pathway [44, 61-64].

In addition to K48-linked ubiquitin modification, the tumor suppressor ARF promotes the K63-mediated polyubiquitination of COMMD1 [65]. K63-polyubiquitination of COMMD1 augments its protein stability and enhances its nuclear levels (Fig. 3). The association between ARF and COMMD1 seems to depend on particular physiological conditions. Upon DNA damage, COMMD1 interacts and colocalizes with ARF. Whether this mechanism is involved in COMMD1-mediated NF-κB inhibition or in other pathways, such as DNA-damage signaling [66], needs to be evaluated.

Apart from the ubiquitination, no other protein modifications of COMMD1 have been reported to date. However, several physiological conditions have been described that affect COMMD1 levels. For instance, chronic copper overload reduces the mRNA and protein levels of COMMD1 in the hepatocellular carcinoma cell line HepG2 [67]. In contrast, increased COMMD1 expression was seen in cells subjected to aspirin [68]. This increase is associated with enhanced RELA-COMMD1 interaction and nucleolar distribution of RELA. Downregulation of COMMD1 desensitizes cells for aspirin-induced apoptosis, possibly through increased expression of NF-κB-mediated anti-apoptotic genes, although these particular changes were not examined in the study of Thoms et al. [68].

Interestingly, the stress-induced small heat-shock chaperone secretory clusterin (sCLU) also mediates the protein levels of COMMD1 [54] (Fig. 3). sCLU is negatively correlated with COMMD1 protein levels, but positively correlated with the expression of various NF-κB-target genes linked with cellular survival. Increased sCLU expression is associated with the survival of cancer cells treated with a wide range of anti-cancer treatments, such as chemotherapy or radiation therapy. In line with these results, decreased expression of COMMD1 is observed in several cancers. Lower COMMD1 expression has been correlated with increased invasion of tumor cells and a reduced survival rate of patients with endometrial cancer [69]. However, whether the expression of sCLU and COMMD1 is inversely correlated within various cancers, or whether this correlation is associated with tumor behavior, needs to be investigated.
Altogether, depending on the physiological conditions, COMMD1 function can be modulated through various mechanisms, including regulation of its protein expression, mRNA expression, and nucleocytoplasmic transport. The biological consequences of these alterations on COMMD1’s function in NF-κB signaling or on other COMMD1-mediated processes require further study.

**COMMD PROTEINS AS BINDING PARTNERS OF CULLINS**

As described previously, all members of the COMMD family have the ability to inhibit NF-κB activity. However, except for COMMD1, the exact mechanisms are still unknown. In addition to COMMD1 [43, 45, 48], all the other COMMD proteins physically associate with different Cullins [56]. Cullin proteins act as core scaffold proteins and together with RING box protein (Rbx1 or Rbx2) form the Cullin-RING-ligases (CRLs). CRLs are the largest family of ubiquitin ligases, and they mediate ubiquitination of a wide range of proteins in various physiological processes [70]. Identification of the ability of COMMD proteins to interact with and regulate different CRLs intensifies the complexity and, presumably, also the specificity of this regulatory mechanism. It is therefore likely that, depending on the physiological conditions, each COMMD protein acts as a hub to control several processes, including NF-κB signaling.

Indeed, as recently indicated, COMMD8 is in complex with the coiled-coil domain-containing protein (CCDC22) and Cullin1 and mediates the protein degradation of IκBα. Depletion of COMMD8 impairs IκBα degradation and, consequently, reduces NF-κB transcriptional activity [71]. Although CCDC22-COMMD1 and CCDC22-COMMD10 protein complexes were also observed, loss of either COMMD1 or COMMD10 does not affect IκBα degradation. This suggests that COMMD8 is essential for the activation of NF-κB, whereas COMMD1 is important for NF-κB termination.

Overall, COMMD proteins interact with specific Cullin-associated complexes and might serve as a hub to regulate the specificity of CRLs.

**COMMD1, A MULTIFUNCTIONAL PROTEIN**

In addition to its role in NF-κB signaling, COMMD1 is also associated with other physiological processes. As mentioned in paragraph 3.1 of this manuscript, COMMD1 was identified as a protein mediating copper metabolism in the liver [44, 64]. Its role in maintaining hepatic copper homeostasis by promoting copper export to the bile was validated in a hepatic Commd1-deficient mouse model [63]. COMMD1 facilitates copper excretion from the liver into the bile, possibly through the copper transporting protein ATP7B [44, 64, 72, 73]. Interestingly, COMMD1 deficiency in various cell lines also affects the transporting capacity of ATP7A, a copper transporting protein that is highly homologous to ATP7B [73]. However, to date, no polymorphisms or mutations in COMMD1 have been found to be associated with human copper overload diseases.

COMMD1 also plays a role in processes like sodium uptake (through regulation of epithelium sodium channel, ENaC, cell surface expression) [74], HIF-1 signaling [59, 60, 69],
cystic fibrosis (through interaction with cystic fibrosis transmembrane conductance regulator, CFTR) [57] and maturation of superoxide dismutase 1 (SOD1) [75]. The common mechanism of COMMD1 action in most of these processes seems to be its role in regulating the protein stability and/or in ubiquitination of its targets. It has also been shown that COMMD1 mediates the trafficking of its targets within the cell [57, 76]. Whether ubiquitination is directly involved in all these processes is still uncertain.

The pleiotropic function of COMMD1 is represented by the lethal phenotype of the Commd1 knockout mouse. In contrast to COMMD1 deficiency in dogs, loss of Commd1 in mice results in early embryonic lethality [59]. These mice die between embryonic stages E9.5 - E10.5. The importance of Commd1 in mouse embryogenesis was confirmed by reintroducing human COMMD1 into the Commd1 knockout mice (B. van de Sluis, unpublished data). Mice deficient in endogenous Commd1, but expressing the human COMMD1 variant are born with the expected Mendelian ratio and do not show any overt phenotype. The exact reason for the discrepancy between dogs and mice is unknown, but it is possible that during embryogenesis in dogs other COMMD proteins can take over the function of COMMD1. Evidence for the lack of non-redundancy of the Commd proteins in mice is illustrated by the fact that genetic deletion of either Commd1, 6, 9 or 10 results in embryonic lethality ([59]; E. Burstein and B. van de Sluis, personal communication). Furthermore, the stage of prenatal death and the morphology of the affected embryos differ between the Commd-deficient embryos, indicating that each Commd protein regulates a specific vital pathway during embryogenesis.

CONCLUDING REMARKS

Since the discovery of NF-κB, much has been learnt about how it is regulated. In recent years, the termination of NF-κB to down-modulate its response has also attracted a lot of attention. As shown by various experimental mouse models, downregulation of NF-κB plays a crucial role in neutralizing inflammation. In this review we have briefly considered several new regulators of NF-κB, paying special attention to the COMMD family of proteins. Currently, most of what we know about the role of this family in NF-κB signaling comes from in vitro studies. These have focused mainly on the mechanisms by which COMMD1, thought to be the prototype of the COMMD family, terminates NF-κB signaling. Yet recent data on COMMD8 in NF-κB modulation suggest that each COMMD protein regulates NF-κB activity in a different manner. This is supported by the different patterns of each COMMD protein-protein network. There is still much to be learned about how this family acts on NF-κB signaling and about its possible roles in many other pathways.

Lack of any catalytic activity suggests that COMMDs act as scaffold proteins to facilitate the assembling of crucial molecular components involved in a number of biological processes, including copper homeostasis, NF-κB and HIF-1 signaling. Nevertheless, the biological relevance of COMMD1 and the other COMMD proteins
in NF-κB-mediated inflammation needs to be investigated. It would be of interest to find any polymorphisms or mutations within the COMMD genes associated with the susceptibility to inflammatory diseases, such as inflammatory bowel disease (IBD). Furthermore, to advance this field, we and our collaborator (E. Burstein) are using genetically engineered mice to elucidate the role of various COMMD proteins (i.e. COMMD1, COMMD6 and COMMD9) in the pathogenesis of different diseases associated with inflammation. We are confident that these mouse models will soon provide new insights into the regulatory mechanisms of inflammation and will help us to understand the functions of this protein family.

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COMMD proteins and NF-κB termination


