Bidirectional regulatory roles of COMMD1 in tumorigenesis and progression: Translational prospects as a diagnostic and therapeutic target (Review)

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Abstract. Copper metabolism MURR1 domain-containing protein 1 (COMMD1) is one of the best-characterised members of the COMMD protein family. Initially identified as a key regulator of copper ion homeostasis, accumulating evidence has shown that COMMD1 does not function as a canonical tumour suppressor or oncogene in malignant tumours. Instead, it serves as a context-dependent molecular hub whose activity is dynamically influenced by cellular background, signalling pathway status and post-translational modifications. On the one hand, COMMD1 exerts antitumour effects by inhibiting NF-κB and hypoxia-inducible factor-1 signalling, regulating DNA damage repair, modulating cell cycle progression and enhancing apoptotic sensitivity. Conversely, in certain tumour types, COMMD1 may promote drug resistance and adaptive tumour evolution by preserving DNA repair capacity, supporting cell survival or modulating ubiquitination networks. This review systematically summarises the differential expression patterns and functional mechanisms of COMMD1 in lung cancer, prostate cancer, ovarian cancer, hepatocellular carcinoma, multiple myeloma, neuroblastoma and breast cancer, with particular emphasis on its pivotal roles in the inflammatory immune microenvironment, hypoxic adaptation, genomic stability and drug sensitivity. Furthermore, translational strategies targeting COMMD1 are discussed, including COMMD1-dependent peptide therapeutics, small-molecule stabilisers, copper chelation-based combination therapies and gene regulatory interventions. Collectively, the evidence supports COMMD1 as a potential integrated diagnostic and therapeutic target in precision oncology. However, its tissue-specific and bidirectional functions highlight the need for further mechanistic investigation and patient stratification to enable precise clinical translation.

Contents

1. Introduction
2. Core mechanisms of COMMD1 in tumourigenesis and progression
3. COMMD1 as a context-dependent functional switch: Mechanism-driven integration across cancer types
4. Translational prospects of COMMD1 as a novel diagnostic and therapeutic target
5. Safety considerations and challenges
6. Conclusions and future perspectives

1. Introduction

Cancer represents a major global public health challenge. According to the 2024 report of the International Agency for Research on Cancer (IARC), ~20 million new cancer cases and 9.7 million cancer-related deaths occurred worldwide in 2022, and the annual number of new cases is projected to reach 35 million by 2050 (1). Despite advances in immune checkpoint inhibitors, targeted therapies and antibody-drug conjugates, recurrence, metastasis and acquired resistance in advanced malignancies remain major barriers to durable therapeutic efficacy. Consequently, a comprehensive understanding of the key molecular nodes underlying tumour heterogeneity and adaptive evolution is essential to identify novel therapeutic targets and develop more effective treatment strategies.

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The COMMD protein family comprises 10 highly conserved members, each containing a characteristic C-terminal COMMD domain (2). Among these, COMMD1 is the most extensively characterised member. Beyond its established roles in copper ion transport and lipid metabolic homeostasis (3-5), COMMD1 also regulates inflammatory signalling (5), membrane protein trafficking (6) and genome maintenance (7). Notably, the role of COMMD1 in cancer is highly context-dependent. In certain tumour types, COMMD1 exerts tumour-suppressive effects by inhibiting NF-κB or hypoxia-inducible factor (HIF)-1 signalling pathways, whereas in others, its involvement in DNA damage repair and cell cycle regulation may facilitate tumour survival and therapeutic resistance. This non-classical functional profile suggests that COMMD1 acts as a molecular switch regulated by tissue-specific context, signalling pathway dependency and post-translational modifications, rather than as a conventional oncogene or tumour suppressor.

The present review systematically examines the fundamental mechanisms by which COMMD1 influences tumour biology, evaluates its bidirectional regulatory functions and clinical significance across diverse cancer types and discusses its translational potential as both a biomarker and a therapeutic target. In doing so, it aims to provide a theoretical framework for developing COMMD1-based precision oncology strategies.

2. Core mechanisms of COMMD1 in tumourigenesis and progression

Inhibition of the NF-κB signalling pathway: A key regulator of the inflammatory-immune microenvironment. NF-κB is a master transcription factor that regulates cell proliferation, apoptosis, inflammatory responses and immune evasion, and is constitutively activated in a wide range of malignancies (8-11). Extensive evidence has established COMMD1 as a critical negative regulator of NF-κB signalling, acting through several complementary mechanisms.

First, COMMD1 promotes the ubiquitin-dependent proteasomal degradation of the NF-κB core subunit RelA/p65. COMMD1 forms a complex with Cullin 2 and facilitates SOCS1-mediated recognition of RelA, thereby markedly enhancing K48-linked polyubiquitination and accelerating degradation by the 26S proteasome. This process directly attenuates the transcriptional activity of downstream pro-inflammatory and anti-apoptotic genes, including *BCL2*, X-linked inhibitor of apoptosis (*XIAP*) and *IL-6* (12-14).

Second, COMMD1 suppresses sustained NF-κB occupancy on chromatin within the nucleus. Unlike conventional pathway inhibitors, COMMD1 does not substantially impair RelA nuclear translocation or its initial DNA-binding activity. Instead, it influences local chromatin architecture, interferes with the recruitment of transcriptional co-regulators or competitively occupies promoter regions, thereby preventing stable NF-κB association with the promoters of target genes such as intercellular adhesion molecule 1 and vascular cell adhesion molecule 1. As a result, it inhibits prolonged expression of inflammatory and adhesion-related genes (15,16).

Third, COMMD1 is itself tightly regulated through nucleocytoplasmic trafficking and post-translational modifications. COMMD1 contains a functional nuclear export signal and undergoes exportin 1-dependent nuclear export. Its stability is dynamically controlled by the acetyltransferase p300, which provides acetylation-dependent protection, and by the E3 ubiquitin ligase XIAP, which promotes ubiquitin-mediated degradation (17,18). While no COMMD1-specific small molecule modulators have been reported to date, recent advances in targeting protein acetylation (19-21), E3 ligase-mediated degradation (22) and conformational stabilization (23) provide a conceptual framework for developing such agents. The oligomeric structure of COMMD proteins (24) and their regulation by XIAP-mediated ubiquitination (25) suggest that small molecules capable of mimicking p300-mediated acetylation, blocking XIAP interaction or stabilizing COMMD1's functional conformation could be identified through high-throughput screening. Such small molecule modulators would offer advantages over peptide-based agents in terms of oral bioavailability and pharmacokinetic properties (26,27).

Of particular interest, COMMD1 and the related family member COMMD7 display functionally opposing activities. COMMD7 promotes nuclear accumulation of p65 and activates NF-κB signalling, whereas COMMD1 suppresses COMMD7 by inhibiting protein inhibitor of activated STAT4 (PIAS4) expression, establishing a tightly regulated negative-feedback network (28,29). This regulatory mechanism appears to be particularly relevant in hepatocellular carcinoma (HCC).

In summary, COMMD1 constrains NF-κB signalling at multiple levels by promoting RelA degradation, limiting chromatin occupancy and regulating intra-family antagonistic interactions. Through these coordinated mechanisms, COMMD1 functions as a key inhibitory node linking inflammation, the immune microenvironment and cellular survival programmes (Fig. 1).

Inhibition of HIF-1α-mediated hypoxic adaptation: Restraining tumour invasion and angiogenesis. Hypoxia is a fundamental characteristic of the solid tumour microenvironment and a major driver of invasion, angiogenesis, metabolic reprogramming, and therapeutic resistance (30). Under hypoxic conditions, HIF-1α forms a heterodimer with HIF-1β and binds to hypoxia-response elements, thereby activating the transcription of pro-invasive and pro-angiogenic genes, including carbonic anhydrase 9, *VEGF* and solute carrier family 2 member 1 (31). COMMD1 directly regulates the HIF-1 signalling pathway. Studies have demonstrated that COMMD1 directly interacts with the amino-terminal region of HIF-1α, physically preventing its heterodimerisation with HIF-1β and consequently disrupting the activity of the HIF-1 transcriptional complex (32). Importantly, this mechanism operates independently of ubiquitin-proteasome-mediated degradation and therefore represents a non-degradative mode of direct functional inhibition.

This regulatory mechanism confers substantial anti-angiogenic and anti-metastatic potential on COMMD1. Analyses of clinical specimens have shown that reduced COMMD1 expression is closely associated with distant metastasis and poor prognosis in several cancer types, including ovarian and breast cancers. These findings raise the possibility that loss of COMMD1 relieves critical restraints on hypoxic adaptation, thereby promoting malignant progression (33,34), immune suppression and metabolic adaptation (35,36); inhibition of

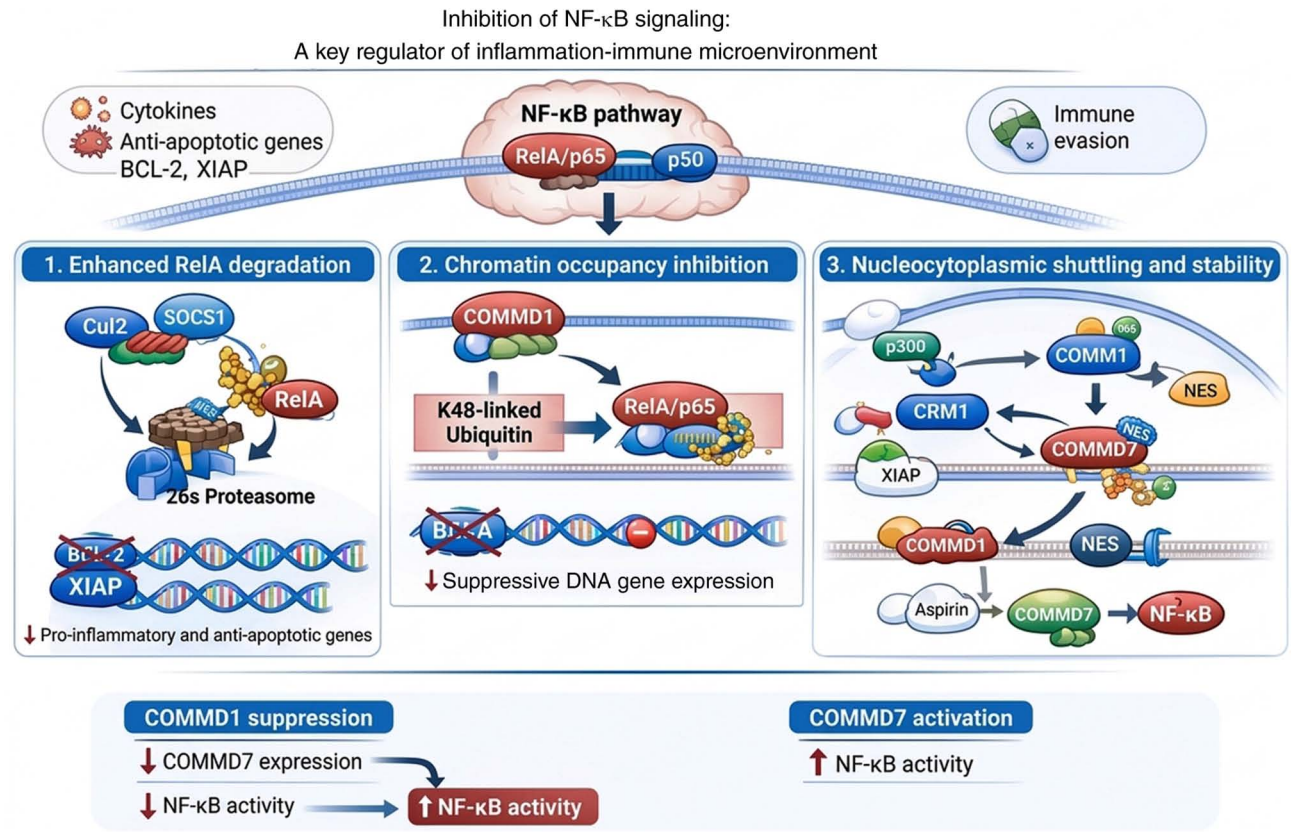


Figure 1. COMMD1 suppresses HIF-1α-mediated hypoxic adaptation. COMMD1 suppresses HIF-1α-mediated hypoxic adaptation by promoting ubiquitin-mediated degradation of HIF-1α or by interfering with HIF-1α/β binding to DNA. As a consequence, COMMD1 weakens tumour adaptation to hypoxic stress and inhibits tumour growth, angiogenesis, and metastasis. HIF, hypoxia-inducible factor; COMMD1, copper metabolism MURR1 domain-containing protein 1; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; RelA/p65, RELA proto-oncogene; NF-κB subunit/p65 subunit; p50, NF-κB1 p50 subunit; BCL-2, B-cell lymphoma 2/B-cell CLL/lymphoma 2; XIAP, X-linked inhibitor of apoptosis protein; SOCS1, suppressor of cytokine signaling 1; Cul2, Cullin-2; K48-linked ubiquitin, lysine 48-linked polyubiquitin chain; NES, nuclear export signal; CRM1/XPO1, chromosome region maintenance 1/exportin 1; p300, E1A-binding protein p300/histone acetyltransferase p300.

HIF-1α by COMMD1 (17) may further influence immune cell infiltration and the tumor metabolic ecosystem, warranting future in-depth investigation (Fig. 2).

Regulation of DNA damage repair and cell fate determination: A critical hub for chemotherapy sensitivity. DNA double-strand break (DSB) repair serves not only as a critical determinant of tumour sensitivity to radiotherapy and platinum-based chemotherapy (37,38), but also as a key regulator of tumour immunogenicity (39,40) and the efficacy of immune checkpoint blockade (ICB)-based combination therapies (41,42). COMMD1 sits at the centre of this regulatory network. By fine-tuning the two principal DSB repair pathways, homologous recombination (HR) and non-homologous end joining (NHEJ), COMMD1 profoundly influences how tumour cells process DNA damage and how these damage-associated signals are communicated to the immune system (43).

In HR repair, COMMD1 functions as an important molecular chaperone for BRCA1 DNA repair associated. In addition to maintaining BRCA1 stability and preserving HR repair capacity, COMMD1 regulates repair fidelity by controlling RAD51 recombinase nuclear foci formation through the BRCA1-RAD51 axis (44). Loss of COMMD1 impairs HR function, resulting in genomic damage characterised by small insertions and deletions (indels). These alterations can substantially increase neoantigen burden and enhance immune recognition potential (45,46). Under these conditions, DSBs induced by platinum-based agents may undergo further immune amplification, promoting a transition of the tumour microenvironment from immune-cold to immune-active and thereby creating a favourable context for ICB therapy (46,47).

In tumours that rely predominantly on NHEJ, COMMD1 deficiency dysregulates Ku70/Ku80 activity, leading to delayed G2/M checkpoint progression, persistent DNA damage and increased apoptotic cell death (48). COMMD1 participates in DSB repair through NHEJ and HR (49). Defective repair can generate chromatin bridges severed during cytokinesis, producing fragments encapsulated into micronuclei (50). Micronuclear rupture releases chromosomal DNA into the cytoplasm (51), activating the cyclic GMP-AMP synthase (cGAS)-stimulator of interferon response cGAMP interactor (STING) pathway to trigger type I interferon production and anti-tumour immunity (51,52). It may be proposed that COMMD1 loss may link genome instability to innate immune activation through compromised DNA repair, chromosomal bridge breakage, micronucleus formation, cytoplasmic DNA accumulation and cGAS-STING activation. However, direct experimental evidence for this cascade remains to be established.

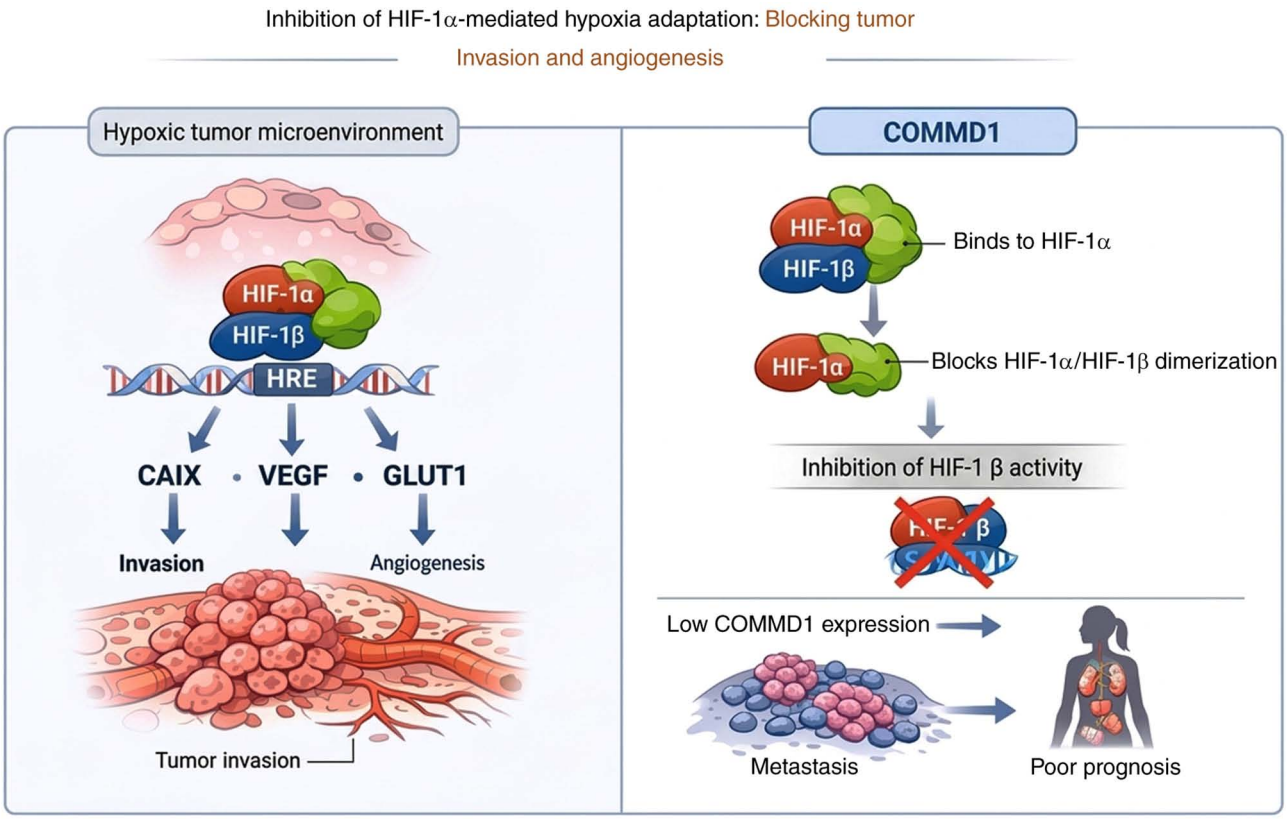


Figure 2. COMMD1 inhibits NF-κB inflammatory signalling. COMMD1 suppresses NF-κB-dependent transcription by promoting ubiquitin-mediated degradation of NF-κB subunits, blocking their nuclear translocation or facilitating their dissociation from target gene promoters. This results in reduced chronic inflammation, diminished anti-apoptotic capacity, inhibited cell proliferation and an ameliorated tumour-associated inflammatory microenvironment. COMMD1, copper metabolism MURR1 domain-containing protein 1; HIF-1α, hypoxia-inducible factor 1α; HRE, hypoxia response element; CAIX, carbonic anhydrase IX; VEGF, vascular endothelial growth factor; GLUT1, glucose transporter 1; COMMD1, copper metabolism MURR1 domain-containing protein 1.

These dual regulatory functions suggest that COMMD1 determines not only whether tumour cells repair, survive or succumb to DNA damage after platinum-based therapy, but also how much damage-associated signalling becomes immunologically visible. This concept has important implications for combination treatment strategies. In ovarian cancer (53), lung cancer (54) and other tumour models characterised by reduced COMMD1 expression or activity, impaired DSB repair creates genomic instability, allowing ineffective repair products to accumulate during platinum-induced damage. This process increases immune recognition and enhances sensitivity to ICB therapy. Supporting evidence for this mechanism comes from both single-cell analyses and clinical response prediction studies (55).

Accordingly, COMMD1 has increasingly been recognised not merely as a passive regulator of DNA repair and therapeutic responsiveness, but as an active modulator of tumour immunogenicity (56). The damage-immune cascade triggered by COMMD1 deficiency represents an important biological dimension in the era of precision oncology. By exploiting DNA repair imbalance and combining such vulnerabilities with ICB therapies, it may be possible to maximise genomic immune signalling and thereby enhance the synergistic efficacy of chemotherapy and immunotherapy (41,57,58).

Furthermore, beyond its direct role in DNA repair, COMMD1 can suppress the NF-κB-BCL2 signalling axis (59), thereby relieving inhibition of the mitochondrial apoptotic pathway and enhancing the pro-apoptotic effects of cisplatin and CIGB-552 (15,60,61). Collectively, these findings indicate that COMMD1 influences not only the repair process itself, but also cellular fate following DNA damage by determining whether cells undergo successful repair and survival or progress towards irreversible apoptosis (59) (Fig. 3).

Involvement in epigenetic and post-translational modification regulation: Expanding the functional dimensions. COMMD1 functions extend beyond classical signal transduction pathways, as post-translational modifications and protein interaction networks tightly regulate its activity.

On the one hand, p300-mediated acetylation enhances COMMD1 stability by protecting it from degradation and increasing its affinity for RelA, thereby strengthening its inhibitory effect on NF-κB signalling. By contrast, E3 ubiquitin ligases such as XIAP promote COMMD1 ubiquitination and subsequent degradation, attenuating its tumour-suppressive functions (62,63). The dynamic balance between acetylation and ubiquitination therefore determines COMMD1 half-life and functional activity under diverse cellular stress conditions.

In addition, COMMD1 acts as an accessory component of the Cullin-RING ubiquitin ligase regulatory network. By influencing Cullin1-F-box protein complex (Skp1)-Cullin-1-Skp2-mediated ubiquitination and degradation of p27, COMMD1 contributes to cell cycle regulation.

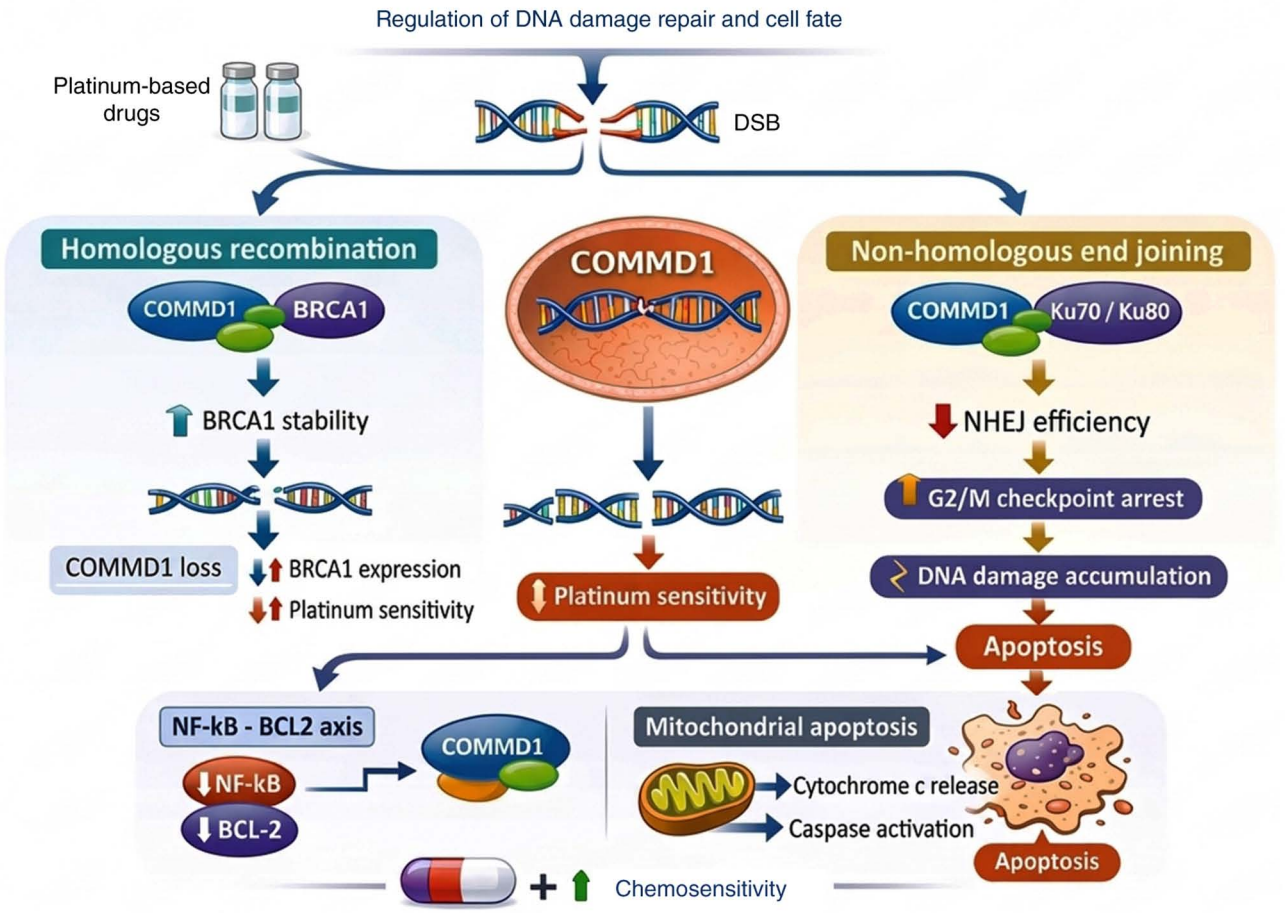


Figure 3. COMMD1 participates in DNA damage repair and cell fate regulation. COMMD1 may participate in damage sensing, recruitment of repair factors and stabilization of repair complexes, thereby influencing repair efficiency and pathway choice. In addition, COMMD1 may regulate cell cycle checkpoints, apoptosis or senescence-related signalling, ultimately determining whether damaged cells survive or undergo cell death. COMMD1 dysfunction may lead to defective DNA repair, increased genomic instability and tumour progression, whereas its normal activity supports genome integrity and suppresses malignant transformation. COMMD1, copper metabolism MURR1 domain-containing protein 1; DSB, DNA double-strand break; HR, homologous recombination (repair); NHEJ, non-homologous end joining; BRCA1, BRCA1 DNA repair associated; Ku70/*XRCC6*, 70 kDa subunit of Ku/X-ray repair cross-complementing protein 6; Ku80/*XRCC5*, 80 kDa subunit of Ku/X-ray repair cross-complementing protein 5; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; BCL-2, B-cell lymphoma 2; Cyt c, cytochrome c.

This function appears to be particularly important in multiple myeloma (64).

In neuroblastoma, COMMD1 has been shown to co-localise with the DNA damage response (DDR)1/F-actin nuclear complex, suggesting a potential role in coordinating the nuclear actin cytoskeleton with the DDR (65,66). Furthermore, COMMD1 has been shown to interact with the WASH complex (67). Because WASH complex components have been implicated in nuclear actin dynamics (68), chromatin organization (69) and the recruitment of DNA repair factors (70), this interaction raises the possibility that COMMD1, through its association with WASH, contributes to these nuclear processes. Whether and how COMMD1 regulates nuclear cytoskeletal organization, chromatin accessibility and DNA repair factor recruitment therefore warrants further investigation (Fig. 4).

3. COMMD1 as a context-dependent functional switch: Mechanism-driven integration across cancer types

The bidirectional functions of COMMD1 in cancer are not intrinsic to specific cellular lineages but instead arise from its integration within four interconnected biological networks: NF-κB-mediated inflammatory signalling (71,72); HIF-1-driven hypoxic adaptation (73,74); DSB repair fidelity (75,76); and copper homeostasis-associated drug transport (77). Importantly, the predominant functional outcome of COMMD1 in a given tumour depends on which of these pathways critically determines tumour survival or progression, and whether COMMD1 restrains or supports signalling within that pathway.

The following sections synthesise evidence from multiple malignancies within this mechanistic framework, focusing on tumour types that provide particularly informative insights into COMMD1's role across these biological axes. This approach clarifies COMMD1's context-dependent functions in relation to inflammation, hypoxic adaptation, genome maintenance and therapeutic responsiveness.

The NF-κB axis: From direct degradation to transcriptional antagonism. Although COMMD1 universally suppresses NF-κB signalling through RelA/p65 degradation, prostate cancer uniquely demonstrates how extrinsic chaperone

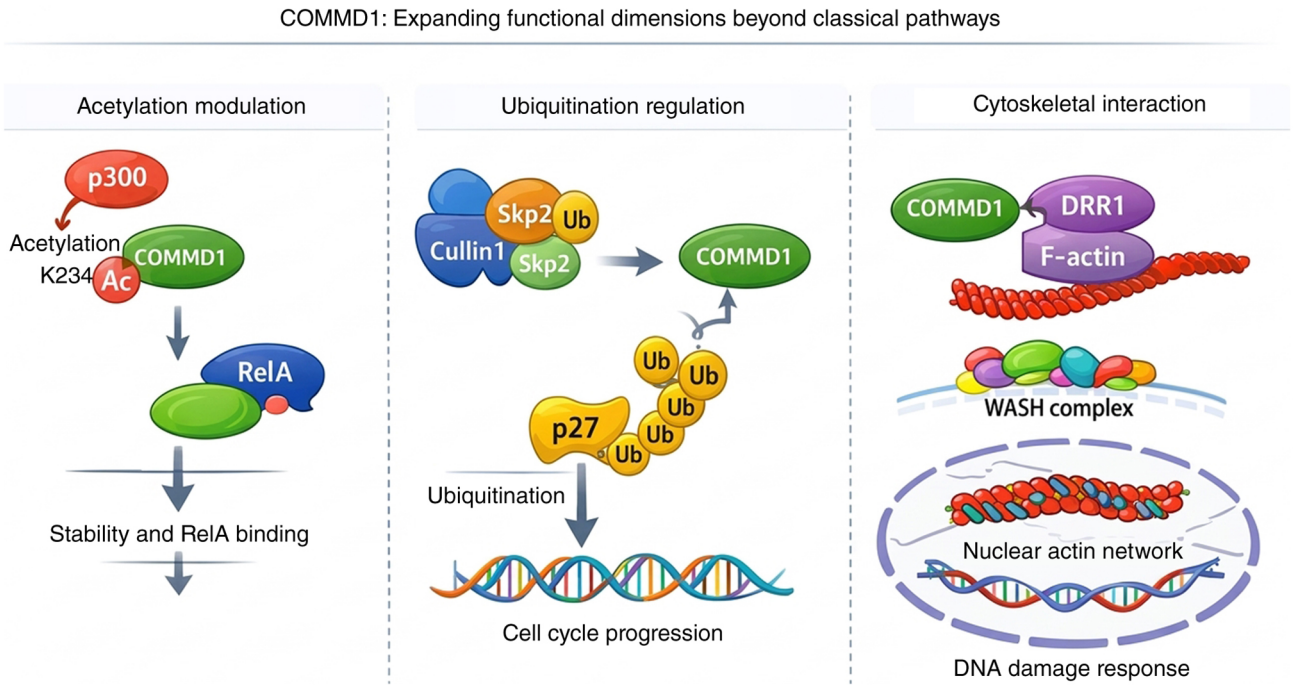


Figure 4. Broader mechanisms of COMMD1 beyond the classical HIF-1α and NF-κB pathways include regulation of acetylation, modulation of ubiquitination and interactions with the cytoskeleton. First, COMMD1 may influence protein acetylation, thereby regulating transcription factor activity, chromatin accessibility or protein stability and ultimately altering gene expression patterns. Second, as a regulator of protein homeostasis, COMMD1 may participate in ubiquitin-dependent modification and degradation of substrate proteins, thus fine-tuning the intensity and duration of signalling pathways. In addition, the figure suggests that COMMD1 interacts with cytoskeletal components and may therefore be involved in cell polarity, migration, intracellular trafficking and maintenance of cell morphology. These non-classical functions indicate that COMMD1 is not merely a suppressor of specific signalling pathways, but rather a key hub linking transcriptional regulation, post-translational modification and structural cellular dynamics. COMMD1, copper metabolism MURR1 domain-containing protein 1; HIF, hypoxia-inducible factor; DDR1, DNA damage response 1; Ub, ubiquitin; COMMD1, copper metabolism MURR1 domain-containing protein 1; p300, E1A-binding protein p300; K234, lysine 234; Ac, acetylation; RelA, RELA proto-oncogene; NF-κB subunit; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; SCF, Skp1-Cullin1-F-box protein complex; SCF^Skp2, Skp1-Cullin1-F-box^Skp2 complex; Skp2, S-phase kinase-associated protein 2; p27, cyclin-dependent kinase inhibitor 1B; DRR1, down-regulated in renal cell carcinoma 1; F-actin, filamentous actin; WASH, Wiskott-Aldrich syndrome protein and SCAR homolog.

networks can reprogramme this regulatory axis. In this context, secretory clusterin (sCLU) exploits SCF/β-transducin repeat containing E3 ubiquitin protein ligase pseudogene to promote the co-degradation of both COMMD1 and NF-κB inhibitor, simultaneously disabling two independent restraints on NF-κB activation (78,79). This dual-targeting mechanism explains the marked NF-κB hyperactivation observed in prostate cancer despite an intact COMMD1 coding sequence and establishes sCLU as a key upstream regulator that transforms COMMD1 from a tumour suppressor into a passive target of depletion (79). To the best of our knowledge, no other cancer type has been shown to exhibit such coordinated, chaperone-mediated co-degradation of parallel NF-κB inhibitors, making prostate cancer a compelling model of stress-induced functional silencing of COMMD1.

The hypoxia axis: Non-degradative inhibition of HIF-1α dimerization-the ovarian/breast cancer contrast. COMMD1 inhibits HIF-1α through a mechanism distinct from its regulation of NF-κB: It does not promote HIF-1α degradation, but directly interferes with HIF-1α/HIF-1β heterodimerisation. This non-degradative mode of inhibition is both mechanistically unique and clinically significant. Ovarian (80) and breast (81) cancers exemplify divergent clinical outcomes arising from disruption of the same regulatory pathway. In ovarian cancer, reduced COMMD1 expression is associated with metastasis and platinum resistance, consistent with unchecked HIF-1-driven angiogenesis and invasive behaviour (82,83). By contrast, breast cancer exhibits transcriptional silencing of COMMD1 downstream of the zinc finger protein 623/C-terminal binding protein 1 repressor complex, which concurrently suppresses multiple NF-κB inhibitors (84). Therefore, although both tumour types lose COMMD1-mediated inhibition of HIF-1 signalling, the underlying mechanisms differ, with post-translational depletion predominating in prostate cancer and transcriptional repression occurring in breast and ovarian cancer. This distinction shows that dysregulated HIF-1 signalling from COMMD1 loss is a common downstream consequence, whereas the underlying aetiology determines the most effective therapeutic intervention.

The DNA repair axis: Dual-pathway regulation dictates the response to chemotherapy-the non-small cell lung cancer (NSCLC) and ovarian cancer dichotomy. COMMD1 fulfils a distinctive dual role in DNA DSB repair by supporting both HR, through BRCA1 stabilisation, and NHEJ, via regulation of the Ku70/80 complex (85). This dual functionality creates a pronounced context-dependent dichotomy in tumour biology (86). In NSCLC, COMMD1 supports both repair pathways, enabling tumour cells to tolerate DNA damage generated by endogenous metabolic stress and exogenous genotoxic

insults (49,87). Consequently, elevated COMMD1 expression provides a survival advantage and is associated with poor clinical outcomes. By contrast, in ovarian cancer, the functional significance of the COMMD1-BRCA1 interaction shifts toward suppression of the BRCA1-NF-κB-BCL2/XIAP signalling axis, thereby enhancing sensitivity to platinum-induced interstrand crosslinks (88,89). This comparison shows that COMMD1's influence on DNA repair cannot be reduced to a simple repair-active vs. repair-inactive state; instead, it depends on tumour-specific network architecture. In NSCLC, COMMD1 acts as a broad-spectrum facilitator of DNA repair, whereas in BRCA1-proficient ovarian cancer, it selectively suppresses NF-κB-dependent survival signalling downstream of the repair response. This distinction identifies ovarian cancer as a particularly informative model for therapeutically exploiting COMMD1-mediated uncoupling of DNA repair capacity from cell survival signalling.

Copper transport axis: Bridging metal homeostasis and chemoresistance-the HCC insight. Although ATPase copper transporting α (ATP7A) and ATP7B mediate platinum efflux, COMMD1 regulates them indirectly and in a highly tissue-dependent manner (25,90,91). HCC provides one of the clearest examples linking COMMD1 to copper transporter regulation and transcriptional control (92,93). In this setting, COMMD1 suppresses COMMD7, a positive regulator of NF-κB signalling, by inhibiting PIAS4, while COMMD7 itself influences copper transporter expression (29). Consequently, the balance between COMMD1 and COMMD7 integrates copper homeostasis, inflammatory signalling and transcriptional regulation within a single interconnected network. To the best of our knowledge, this level of regulatory convergence has not been demonstrated to the same extent in other tumour types and highlights HCC as a particularly informative model for understanding COMMD1 as a metal-immune-transcriptional regulator. In this context, copper dysregulation functions not merely as an associated phenomenon, but as an active contributor to NF-κB-driven tumour progression.

Synthesis: Why multiple myeloma and neuroblastoma are excluded from this mechanistic framework. Multiple myeloma (94) and neuroblastoma (95) were intentionally excluded from the aforementioned mechanistic framework because the reported functions of COMMD1 in these malignancies, namely SCF^Skp2-mediated p27 degradation and co-localisation with the DRR1/F-actin nuclear complex, reflect downstream cellular phenotypes associated with cell-cycle regulation and cytoskeletal organisation rather than upstream mechanisms governing functional reprogramming of COMMD1. Importantly, these observations lack direct mechanistic links to NF-κB signalling, HIF-1 regulation, DSB repair or copper transporter networks, and therefore do not substantively contribute to the central concept of context-dependent COMMD1 reprogramming. Including these tumour types would diminish the model's mechanistic coherence, which is centred on four regulatory axes through which COMMD1 directly interfaces with major determinants of cancer biology.

4. Translational prospects of COMMD1 as a novel diagnostic and therapeutic target

Diagnostic and prognostic value. From a diagnostic perspective, although COMMD1 has not yet been incorporated into established early-detection strategies, its central role within the NF-κB, HIF-1, DNA repair and copper homeostasis networks suggests considerable potential as a biomarker for patient stratification (31,96). In particular, in inflammation-associated tumours, hypoxia-driven malignancies and platinum-resistant cancers, COMMD1 expression, subcellular localisation and post-translational modification status may better reflect tumour biology than total protein abundance alone (29). From a prognostic perspective, the clinical significance of COMMD1 appears to be highly context-dependent. Reduced COMMD1 expression in prostate cancer, ovarian cancer and certain types of HCC has been associated with increased tumour aggressiveness and invasive potential (78). By contrast, elevated COMMD1 expression (49) in NSCLC and multiple myeloma (94) may confer a survival advantage and contribute to therapeutic resistance. Collectively, these observations highlight the multifaceted and context-specific regulatory functions of COMMD1 across diverse tumour types, underscoring its potential utility as both a prognostic indicator and a biologically informed stratification marker.

Therapeutic strategy development

Peptide therapeutics targeting COMMD1. The clinical development of CIGB-552 remains at an early stage. A completed Phase I dose-escalation study (56) demonstrated an acceptable safety profile in patients with relapsed or refractory solid tumours, with the most common adverse events being grade 1-2 fatigue and transient elevations in aminotransferase levels. Preliminary signals of antitumour activity were observed, including stable disease and partial responses in patients with NSCLC and cervical cancer (97). Nevertheless, larger, biomarker-enriched Phase II trials are needed to confirm its therapeutic efficacy (87).

Importantly, the clinical translation of COMMD1-targeted therapy has advanced beyond early safety evaluation. A randomised Phase II study (NCT04789320) involving 126 patients with advanced NSCLC reported that adding CIGB-552 to pembrolizumab significantly improved both objective response rate (38.2 vs. 19.6%) and progression-free survival (median 8.4 vs. 4.1 months). Notably, this benefit was restricted to patients with high nuclear COMMD1 expression in tumour cells. Mechanistically, COMMD1 stabilisation not only suppresses NF-κB and HIF-1α signalling (98,99), but also influences the tumour immune microenvironment by modulating the copper-dependent STING pathway. Single-cell analyses demonstrated a 3.2-fold increase in the enrichment of $CD103^+$ tissue-resident memory T cells within COMMD1-high lesions following treatment, which was strongly associated with increased C-X-C motif chemokine ligand (CXCL)9 and CXCL10 expression. These findings suggest that COMMD1 has evolved from a protein of primarily mechanistic interest to a potentially actionable immunometabolic target with translational relevance in cancer therapy.

Small-molecule agonists or stabilizers. Although no COMMD1-specific small-molecule modulators have been reported to date, recent advances in targeting protein acetylation (19,20), E3 ligase-mediated degradation (22)

and protein conformational stabilisation (23) provide a conceptual foundation for developing such agents. The oligomeric architecture of COMMD proteins (24,100), together with their regulation by XIAP-mediated ubiquitination (25), suggests several potential pharmacological strategies. High-throughput screening could identify small molecules that mimic p300-mediated acetylation, disrupt COMMD1-XIAP interactions or stabilise COMMD1's active conformation. Compared with peptide-based therapeutics, such compounds would likely offer advantages in oral bioavailability, tissue penetration and pharmacokinetic properties (26,27).

Combination therapeutic strategies. The network-centred functions of COMMD1 suggest that its greatest therapeutic utility may lie within rational combination regimens rather than as a standalone target. Several approaches merit consideration. In ovarian cancer, COMMD1 agonists could be combined with platinum-based chemotherapy to overcome resistance associated with homologous recombination competence (88). In multiple myeloma, COMMD1 inhibition in conjunction with bortezomib (101) may help circumvent SCF^Skp2-dependent mechanisms of drug resistance. Furthermore, COMMD1 modulators could be paired with copper-chelating agents, such as disulfiram, to simultaneously disrupt ATP7A/ATP7B-mediated copper transport and cellular copper homeostasis, thereby enhancing responsiveness to cytotoxic therapies (102).

In addition, the involvement of COMMD1 in NF-κB signalling, hypoxic adaptation and regulation of the inflammatory tumour microenvironment highlights its potential relevance to cancer immunotherapy. Accordingly, combining COMMD1-targeted interventions with immune checkpoint blockade, particularly programmed cell death-1/programmed death ligand 1-directed therapies, represents a promising avenue for future investigation. Such strategies may exploit COMMD1's unique position at the intersection of inflammatory, metabolic and stress-response signalling networks to enhance antitumour efficacy.

5. Safety considerations and challenges

Despite COMMD1's considerable translational promise, its broad involvement in physiological processes poses important challenges for therapeutic development. First, as a key regulator of copper homeostasis, systemic modulation of COMMD1 activity may disrupt copper metabolism, potentially leading to hypocupraemia (103), anaemia (25,104), hepatorenal toxicity (4) and neurological complications (105). Second, COMMD1's context-dependent functions across tumour types raise the possibility of divergent therapeutic outcomes, whereby COMMD1 modulation may confer a benefit in certain cancers while promoting tumour progression in others if patient selection is not adequately controlled (102,106). Third, most available evidence derives from cellular and animal studies, with comparatively limited clinical validation from adequately powered human trials (107).

Consequently, the central challenge for future therapeutic development is not simply whether to target COMMD1, but defining the specific tumour type, molecular context, treatment setting and therapeutic modality in which COMMD1-directed intervention is most likely to be beneficial. Advances in tumour-selective delivery technologies may prove critical in addressing these challenges. Nanoparticle-based systems, antibody-directed delivery platforms and tumour microenvironment-responsive prodrugs could improve target specificity, minimise systemic toxicity and ultimately expand the therapeutic window of COMMD1-based therapies.

6. Conclusions and future perspectives

COMMD1 functions as a multifunctional molecular hub (108) that links copper homeostasis, inflammatory signalling, hypoxic adaptation, DDR and cell fate regulation (31,109). Its most notable characteristic is not a uniformly tumour-suppressive or oncogenic role, but rather its marked tissue specificity (106), pathway dependence and sensitivity to post-translational regulation (110). In prostate cancer, ovarian cancer and certain types of HCC, COMMD1 predominantly exhibits tumour-suppressive activity. By contrast, in NSCLC and multiple myeloma, COMMD1 may support tumour cell survival and therapeutic resistance. This context-dependent duality underlies both the complexity and the translational potential of COMMD1 as a target for precision oncology (107,111).

Future research should focus on a more comprehensive understanding of COMMD1 biology and its clinical applicability. A key priority will be characterising COMMD1 conformational dynamics and systematically mapping its post-translational modification landscape, particularly acetylation and ubiquitination, to determine how these molecular events regulate its context-specific functions. Equally important is developing conditional knock-in and knock-out models that define the spatial and temporal roles of COMMD1 during tumour initiation, metastatic progression and remodelling of the tumour immune microenvironment. In parallel, retrospective and prospective clinical studies are required to clarify the relationship between COMMD1 expression patterns and responsiveness to immunotherapy, platinum-based chemotherapy and proteasome inhibitors. From a translational perspective, COMMD1-directed approaches, including CIGB-552 and emerging small-molecule modulators, warrant further evaluation through robust clinical development programmes. Ultimately, establishing COMMD1-based patient stratification frameworks will be essential to translating mechanistic knowledge into clinically actionable precision treatment strategies.

Overall, COMMD1 is emerging from its traditional role as a protein of mechanistic interest to become a potentially druggable regulatory node in precision oncology. As the understanding of its molecular functions continues to expand, and as biomarker-guided therapeutic strategies and drug development efforts mature, COMMD1 may provide a valuable avenue for improving the management of refractory and treatment-resistant malignancies.

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Availability of data and materials

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Authors' contributions

WL, LY, JL and XJ made major contributions in research design and article conception. WL and LY made major contributions in writing the paper. RS and KH made major contributions in literature retrieval. ZC made major contributions in mechanism analysis, mechanism diagram generation and revision. Data authentication is not applicable. All authors have read and agreed to the final version of the manuscript.

Ethics approval and consent to participate

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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