Review Article

Canonical and noncanonical NF-κB signaling in uveal melanoma: mechanisms, microenvironment, and therapeutic modulation

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ABSTRACT

Background: Uveal melanoma (UM) is an aggressive intraocular malignancy with high metastatic potential to the liver and poor prognosis. The nuclear factor kappa B (NF-κB) pathway, comprising the canonical and noncanonical branches, has been involved in UM development, tumor-microenvironment communication, and drug resistance. This review consolidates the evidence for NF-κB involvement in UM pathogenesis and therapeutic target value.

Methods: A comprehensive search of PubMed/MEDLINE, Embase, Web of Science, Scopus, and the Cochrane CENTRAL database was performed from inception to June 2025. Studies investigating NF-κB activation, functional dependencies, genetic or microenvironmental modulators, or therapeutic interventions in UM were eligible. Included designs comprised original observational or experimental research, including mechanistic *in vitro* studies, animal models, and human tissue–based prognostic or correlative studies. English-language articles and relevant review studies addressing the research question were considered. Exclusion criteria included editorials, commentaries, conference abstracts with insufficient data, case reports lacking mechanistic insights, non-UM cancers without validated UM models, studies mentioning inflammation or NF-κB targets without direct NF-κB readouts, and those using pleiotropic inhibitors without genetic validation or pathway-specific evidence. Appropriate design-specific tools were applied to assess risk of bias.

Results: Canonical NF-κB signaling is mechanistically related to UM cell survival, proliferation, and migration, as shown by pharmacologic inhibition like BAY11-7082, and niclosamide and genetic modulation like microRNA-9. Noncanonical signaling is associated with invasive, immune-replenished tumors and liver metastasis yet has limited direct functional data. Deficiency in BRCA1-associated protein-1 (BAP1) and tumor necrosis factor alpha-enriched microenvironments control NF-κB activity, but there is conflicting data on the function of BAP1. Therapeutic targeting of NF-κB consistently suppresses UM phenotypes *in vitro* and *in vivo*, but pleiotropic inhibitor effects require confirmation.

Conclusions: NF-κB signaling, particularly the canonical branch, is required for UM malignancy, while noncanonical signaling is linked with high-risk features. Branch-specific genetic manipulations and clinically relevant models should be employed in future research to maximize therapeutic strategies.

KEYWORDS

intraocular melanoma, NF-kappaB, nuclear factor kappa B, tumor microenvironments, BAP-1 protein, human, Brca1 associated protein 1, mouse, BRCA1 associated deubiquitinase 1 protein, rat, therapeutic

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INTRODUCTION

Uveal melanoma (UM) is the most common adult primary intraocular malignancy, with predominant hematogenous spread to the liver; available systemic therapies are extremely scarce and prognosis is poor [1, 2]. This therapeutic challenge has stimulated intense investigation of tumor-intrinsic survival mechanisms and tumor-microenvironment interactions that may be potential candidates to target therapy. Of these, nuclear factor-kappa B (NF-κB) signaling—through a canonical pathway (inhibitory kappa B kinases [IKK]β/IκBα/RelA [p65]:p50) or a noncanonical pathway (NF-κB-inducing kinase [NIK]/IKKα/p100→p52/RelB)—has been a recurring theme across patient tissue, cell models, and preclinical models in UM [3–5].

Early transcriptomic comparisons between primary UM and liver metastases identified NF-κB family involvement, including NF-κB2 upregulation with immunohistochemical validation in samples from patients with liver metastases [6], indicating involvement of noncanonical signaling in metastatic status [3, 6, 7].

Follow-up analysis of primary tumors and metastases confirmed expression of NF-κB members (NF-κB1, NF-κB2, RelA [p65], RelB, NIK) and reported elevated NF-κB2, RelB, and NIK mRNA levels in metastases, suggesting noncanonical pathway activation in advanced disease [3]. Clinical-pathologic series also reported that canonical NF-κB pathway readouts and constitutive c-REL expression were associated with outcome parameters, substantiating clinical relevance of NF-κB activity in UM [8–10].

By inhibiting NF-κB activating pathways, pharmacologic intervention such as BMS-345541 and dehydroxymethylepoxyquinomicin (DHMEQ) suppressed NF-κB activation and facilitated apoptosis in metastatic UM-derived cell lines [3, 11, 12]. NF-κB pathway inhibitor BAY11-7082 reduced RelA (p65) nuclear translocation, induced apoptosis, suppressed migration *in vitro*, and curtailed gastric cancer xenograft growth *in vivo* [5, 13]. Drug repositioning with niclosamide revealed strong antitumor activity in UM through NF-κB inhibition, reactive oxygen species (ROS)-mediated apoptosis, matrix metalloproteinase (MMP)-9-dependent invasion blockade, and suppression of Wnt/β-catenin pathway, effects validated *in vitro* and *in vivo* UM xenograft models [4].

Complementing these pharmacological results, microRNA-9 (miR-9) directly targeted NF-κB1 (p50/p105) to suppress tumor invasion and decrease NF-κB-regulated effectors—MMP-2, MMP-9, and vascular endothelial growth factor A (VEGFA) [14, 15]. Other small-molecule studies using ergolide [16, 17] reported anti-UM activity and proteomic alterations [16], besides suppression of NF-κB activation [17]. However, the extent of NF-κB pathway mediation in these changes warrants further investigation [16, 17].

In UM, an inflammatory phenotype characterized by increased infiltration of lymphocytes and macrophages, along with elevated human leukocyte antigen (HLA) class I and II expression, is associated with poor prognosis that is often linked to monosomy of chromosomes-3. It may be driven in part by hypoxic conditions within the tumor microenvironment [18]. This inflammatory context provides important insight into the role of NF-κB signaling in UM. Increased expression of NFκB1 and NFκB2 has been observed in monosomy of chromosome-3/BRCA1-associated protein-1 (BAP1)-negative tumors [19]. Moreover, tumors with high HLA class I expression and dense leukocyte infiltration, both markers of poor prognosis [19, 20], are enriched for NF-κB family members, particularly NFκB1, NFκB2, and RelB [19].

Aqueous humor samples from eyes with UM show elevated cytokine levels, indicating macrophage infiltration [21]. Functional enrichment analysis of gene expression in UM further indicates that macrophage subset 2 is associated with upregulated pathways related to the inflammatory response, tumor necrosis factor α (TNF-α) signaling via NF-κB, and hypoxia [22]. Inhibition of TNF-α signaling is shown to prevent NF-κB activation in hepatocytes and early-stage hepatocellular carcinoma, and—similarly to direct NF-κB inhibition—leads to increased hepatocyte apoptosis and reduced tumor multiplicity, highlighting the pro-tumorigenic role of this pathway [4, 23]. These findings highlight NF-κB as a central player in tumor cell survival, progression, and metastasis in UM [3, 19].

The relationship between BAP1 status and NF-κB signaling is not well understood. Although gene expression analyses in UM have linked monosomy of chromosome-3/BAP1-negative tumors to high expression of NF-κB components and HLA [19], a recent bioinformatic and cellular analysis indicates that BAP1 mutations inhibit the NF-κB signaling pathway and reprogram macrophage-associated cytokine expression. Reconstitution of NF-κB partially reverses these effects [24]. These conflicting findings highlight the need to investigate the potential role of BAP1 in both the canonical and noncanonical NF-κB pathways, using parallel analyses of BAP1-positive and BAP1-deficient UMs [19, 24, 25].

Therapeutically, these data suggest that NF-κB is both a target and a site of interaction with oncogenic $G\alpha_{q/11}$-mediated pathways (protein kinase C [PKC]/mitogen-activated protein kinase [MAPK]/yes-associated protein [YAP]) in UM, yielding multiple points of intervention—directly on IKK/RelA (p65) or indirectly upstream—to modulate survival and inflammatory outputs [1, 2, 3, 16]. Although some current evidence relies on pleiotropic inhibitors, establishing definitive causality and translational potential will require rigorous genetic loss-of-function and rescue approaches, precise pathway readouts, and models that faithfully recapitulate liver-tropic metastasis and microenvironmental drivers [1, 5, 15, 16].

In this comprehensive review, we synthesize and critically assess the evidence for canonical and noncanonical NF-κB signaling in UM along four axes: (i) pathway activation in primary tumors and metastases; (ii) tumor-intrinsic mechanistic dependencies and phenotypes; (iii) microenvironmental and genetic modulators, including BAP1 status and HLA/inflammatory programs; and (iv) therapeutic modulation with pharmacologic and genetic interventions. We delineate concordant and discordant regions (e.g., the BAP1/NF/κB axis) and assess methodological factors that determine the robustness of current conclusions [7–9, 11, 17, 18, 20, 22, 23, 25]. Although NF-κB signaling has been implicated in ocular surface malignancies such as conjunctival melanoma and ocular surface squamous neoplasia, the evidence base reviewed here is primarily derived from studies on UM. Accordingly, we focus on UM while highlighting the need for future research using validated conjunctival and ocular surface models to address existing gaps [1, 26, 27].

This review outlines current understanding of NF-κB signaling in UM and its implications for therapy and modeling.

METHODS

This comprehensive review was designed and reported with partial compliance with the PRISMA 2020 statement [28]. Specifically, we adopted the PRISMA checklist and flow diagram to ensure a systematic approach to study identification, screening, eligibility evaluation, and inclusion.

We framed review questions as follows, to delineate canonical and noncanonical NF-κB signaling in UM in both tumor-intrinsic and microenvironmental contexts, and in therapy modulation.

1. What patient and experimental UM model evidence suggests activation of canonical NF-κB (IKKβ/IκBα/RelA [p65]:p50) and/or noncanonical NF-κB (NIK/IKKα/p100→p52/RelB)?
2. To what extent are UM malignant phenotypes dependent upon NF-κB signaling?
3. How do UM-applicable genetic mutations (e.g., *BAP1* status, activation of GNAQ/GNA11 pathway) and microenvironmental cues (e.g., TNFα/interleukin [IL]-1β, infiltration of leukocytes, hepatic niche signals) control NF-κB branch activation and outputs?
4. Which interventions regulate NF-κB signaling directly or indirectly, and to what extent and degree of consistency?

We defined eligibility criteria as PECO(S) components modified for preclinical and clinical studies. Population consisted of human UM tissues (metastases and primary tumors), patient-derived samples, UM cell lines and organoids, and UM animal models (xenografts, zebrafish, or murine models). The exposure/intervention was activation or perturbation of NF-κB signaling—canonical or noncanonical—such as cytokine stimulation, genetic alteration of NF-κB components, or treatment with agents known to affect the NF-κB pathway. Comparators were vehicle controls or untreated, non-targeting genetic controls, or other pathway perturbations. Outcomes were split into input indicators and output indicators (below). In addition to primary research articles, relevant reviews were also included to provide a broader understanding of the topic.

Study designs included original observational and experimental studies: mechanistic *in vitro*, animal experiments, and human tissue-based prognostic or correlative studies. English-language articles from database inception through June 2025 were explored, including relevant review studies that addressed the research question. Excluded were editorials, commentary, conference abstracts with limited data, case reports without mechanistic analysis, and non-uveal cancer studies unless bona fide UM models were present; studies with inflammation or NF-κB targets reported but no direct NF-κB readout; and studies with pleiotropic inhibitors alone and no supporting genetic validation or pathway readouts.

Inclusion criteria comprised original observational and experimental studies that documented experimental or clinical manipulations used to induce or inhibit NF-κB signaling. These manipulations included cytokine or ligand stimulation (e.g., TNFα, IL-1β, Toll-like receptor agonists), genetic manipulation of NF-κB pathway members (e.g., RelA [p65], RelB, NF-κB1, NF-κB2, NIK, or IKKβ knockdown, knockout, or overexpression), pharmacologic activators or inhibitors with specified targets (e.g., IKKβ inhibitors, NF-κB essential inhibitors NEMO-binding agents, mitogen-activated protein/extracellular signal-regulated kinase MEK inhibitors, PKC inhibitors), and microenvironmental or genetic conditions (e.g., BAP1 status, monosomy 3, GNAQ/GNA11 mutations, hepatic stromal co-culture).

Output measures captured direct NF-κB pathway activity and downstream biological effects. Readouts of direct pathway activity included IκBα phosphorylation/degradation, RelA (p65) or RelB nuclear localization, κB-reporter activity, electromobility shift assay (EMSA) with subunit identification, and chromatin immunoprecipitation (ChIP) on κB-regulated promoters. Downstream outputs were expression of conventional NF-κB target genes including BCL2, BIRC2, BIRC3, MMP family genes and cytokine/chemokine genes (proteins: BCL2, cellular inhibitor of apoptosis proteins [cIAPs], MMPs, and cytokines/chemokines), HLA class I and II and peptide-loading apparatus, tumor-cell phenotypes (viability, apoptosis, proliferation indices, migration/invasion), immune infiltration quantities in human tumors, and *in vivo* tumor growth or metastasis measures. Studies lacking at least one direct NF-κB readout experiment were excluded unless pathway-selective genetic perturbation was paired with coherent downstream effects that were reversed by rescue.

We thoroughly searched a number of bibliographic databases to obtain maximal coverage of fundamental, translational, and clinical studies. Databases searched included MEDLINE through PubMed, Embase, Web of Science Core Collection, Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL). In order to access gray literature and avoid time-lag bias, we screened reference lists of included studies and reviews and performed forward citation tracking of landmark papers. Preprint servers (bioRxiv and medRxiv) were also searched for recent mechanistic studies; preprints were only retained if methods and data were clearly explained for risk-of-bias assessment and were marked as non-peer-reviewed.

Search strategies were developed with an information specialist and tailored to each database using controlled vocabulary and free-text terms for UM and NF-κB signaling. Strategies combined terms for UM and its anatomic subtypes with terms for NF-κB, Rel family members, and key pathway nodes, using Boolean operators and field restrictions. No study design filters were applied at the search stage (Table 1).

All the records were imported into a reference manager, and duplicates were removed through exact and fuzzy matching on authors, titles, and DOIs. Two reviewers independently screened titles and abstracts against eligibility criteria. Articles deemed to be potentially relevant by one of the two reviewers proceeded to full-text assessment. Two reviewers independently assessed full texts, with discrepancies resolved by consensus or by a third reviewer. Exclusion reasons on the full-text stage were documented verbatim (e.g., not UM, no readout for NF-κB, not enough methodological detail, no direct NF-κB readout, used pleiotropic inhibitors without genetic validation, insufficient data, non-English language). Inter-rater agreement (Cohen's kappa) was determined for both screening stages.

Risk of bias and quality assessment: As the designs were heterogeneous, we employed design-appropriate tools. In nonrandomized and randomized animal trials, we applied the SYRCLE risk-of-bias tool and assessed ARRIVE reporting items compliance (blinding, randomization, allocation concealment, sample size justification, attrition). For mechanistic *in vitro* studies, we utilized a pre-specified checklist according to NIH study domains of quality and relevant *in vitro* assessment frameworks with emphasis on UM cell line authentication, mycoplasma testing, replication, adequate controls, dose-response, inhibitor selectivity, genetic verification, blinded quantitation, and statistical rigor. For observational tissue studies involving humans with NF-κB readouts and clinicopathologic outcomes reported in association, we applied ROBINS-I for nonrandomized exposures and QUIPS for prognostic factors based on confounding control, outcome measurement, and completeness of data. Two independent reviewers allocated each study a domain-level and overall risk-of-bias rating; discrepancies were settled by a third reviewer.

Table 1. Search strategies for bibliographic databases

Database	*Complete Search Syntax*
PubMed	*("Uveal Neoplasms"[Mesh] OR "Choroid Neoplasms"[Mesh] OR "uveal melanoma"[tiab] OR "choroidal melanoma"[tiab] OR "ciliary body melanoma"[tiab] OR "ocular melanoma"[tiab]) AND ("NF-kappa B"[Mesh] OR "NF-κB"[tiab] OR "NF-kappaB"[tiab] OR "NFKB1"[tiab] OR "NFKB2"[tiab] OR "RELA"[tiab] OR "RelA"[tiab] OR "RELB"[tiab] OR "c-Rel"[tiab] OR "p65"[tiab] OR "p50"[tiab] OR "p52"[tiab] OR "IKK"[tiab] OR "IKKβ"[tiab] OR "IKK alpha"[tiab] OR "IκBα"[tiab] OR "NEMO"[tiab] OR "MAP3K7"[tiab] OR "TAK1"[tiab] OR "NIK"[tiab] OR "MAP3K14"[tiab] OR "κB-luciferase"[tiab] OR "kappaB reporter"[tiab]).*
Embase	*('uveal melanoma'/exp OR 'uveal melanoma':ti,ab OR 'choroidal melanoma':ti,ab OR 'ciliary body melanoma':ti,ab OR 'ocular melanoma':ti,ab) AND ('nf kappa b'/exp OR 'nf kappa b':ti,ab OR 'nf-κb':ti,ab OR nfkB1:ti,ab OR nfkB2:ti,ab OR rela:ti,ab OR relb:ti,ab OR 'c rel':ti,ab OR p65:ti,ab OR p50:ti,ab OR p52:ti,ab OR 'ikk beta':ti,ab OR 'ikk alpha':ti,ab OR nemo:ti,ab OR 'iκb alpha':ti,ab OR 'tak1':ti,ab OR 'map3k7':ti,ab OR 'nik':ti,ab OR 'map3k14':ti,ab OR 'kappa b reporter':ti,ab). Filters were limited to human, animal, and in vitro studies with no date restriction; conference abstracts were excluded at screening.*
Web of Science	*TS=("uveal melanoma" OR "choroidal melanoma" OR "ciliary body melanoma" OR "ocular melanoma") AND TS=("NF-κB" OR "NF-kappaB" OR NFKB1 OR NFKB2 OR RELA OR RELB OR "c-Rel" OR p65 OR p50 OR p52 OR IKK OR "IκBα" OR NEMO OR TAK1 OR NIK OR "kappaB reporter").*
Scopus	*TITLE-ABS-KEY("uveal melanoma" OR "choroidal melanoma" OR "ciliary body melanoma" OR "ocular melanoma") AND TITLE-ABS-KEY("NF-κB" OR "NF-kappaB" OR nfkB1 OR nfkB2 OR rela OR relb OR "c-rel" OR p65 OR p50 OR p52 OR ikk OR "iκbα" OR nemo OR tak1 OR nik OR "kappaB reporter").*
CENTRAL	*("uveal melanoma" OR "choroidal melanoma") in Title/Abstract/Keywords AND ("NF-κB" OR "NF-kappaB" OR RELA OR RELB OR NFKB1 OR NFKB2 OR IKK OR "IκBα" OR TAK1 OR NIK).*

We piloted an improved data extraction form before using it. Two reviewers independently extracted bibliographic data, study design, UM models and origin (genetic drivers and BAP1 status where known), experimental conditions and input markers (stimuli, genetic manipulations, pharmacologic agents with targets and concentrations), direct NF-κB readouts (type of assay, timepoints, branch attribution), downstream outputs (gene/protein expression, proliferation/viability, apoptosis, migration/invasion, HLA expression, cytokines/chemokines), *in vivo* endpoints (tumor growth, metastasis, survival), statistical analysis, effect estimates with measures of variance, and funding/conflict-of-interest statements. For pharmacologic experiments we also extracted inhibitor selectivity data and any genetic rescue data. We corresponded with authors once for critical missing data; if data could not be obtained, the study was retained and limitations recorded.

For data synthesis and analysis, we prespecified a hierarchical synthesis. We initially carried out a qualitative, branch-specific synthesis mapping each study to canonical vs. noncanonical NF-κB activation, cell compartment(s), and strength of evidence by direct pathway readout and genetic validation. We then classified phenotypic outcomes by domain (survival/proliferation, invasion/migration, antigen presentation, cytokine programs, *in vivo* growth/metastasis) and tabulated direction and consistency of effects upon NF-κB perturbation. Sources of heterogeneity would be examined with subgroup analyses according to NF-κB branch (canonical vs. noncanonical), type of perturbation (genetic vs. pharmacologic), model system (*in vitro* vs. *in vivo*), and genetic context (BAP1 status). In cases where quantitative synthesis was not feasible because of heterogeneity or poor reporting, we presented structured narrative summaries and, where feasible, vote counting by effect direction with harvest plots. Sensitivity analyses included exclusion of high-risk bias studies, exclusion of studies based solely on the use of pleiotropic inhibitors without genetic confirmation, and leave-one-out analyses for all meta-analyses undertaken. Publication bias was to be assessed by funnel plots and Egger's test if ten or more studies contributed to a meta-analysis, otherwise we described small-study effects narratively.

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RESULTS

Study Selection Process

The initial database and additional source search yielded 325 and 20 records, respectively. All studies retrieved from additional sources were excluded, as none met the inclusion criteria. After duplicates (85) were removed, 240 records were title- and abstract-screened (Figure 1). During the screening stage, 195 records were excluded for reasons detailed in the PRISMA flow chart (Figure 1). Full-text review was conducted for 45 articles, 30 of which were excluded based on the criteria outlined in the same figure.

Fifteen studies met all eligibility criteria [1, 3–6, 9, 10, 14, 16, 18–21, 24, 29] and were included in the comprehensive review. The whole selection process is illustrated in Figure 1.

We carried out the data extraction with a piloted, standardized form and two independent reviewers, as planned. Of the 15 records, 13 were reports of primary data [3–6, 9, 10, 14, 16, 19–21, 24, 29] and two were narrative reviews [1, 18] (Table 2). Based on the messages of the included studies, we summarized the evidence in Tables 3–6, covering NF-κB activation (Table 3), functional dependence of tumor phenotypes (Table 4), genetic and microenvironmental modulators (Table 5), and therapeutic modulation of NF-κB signaling in UM (Table 6).

Four studies had included *in vivo* efficacy or colonization models (three murine xenografts and one zebrafish), five were mechanistic *in vitro* alone, four were human observational cohorts/tissue studies. Canonical NF-κB readouts in UM cells were variably detected by RelA (p65) nuclear translocation and cytokine-activated stimulation, while noncanonical stimulation was implied by NF-κB2, RelB, and NIK expression in tumors and liver metastases. Pharmacologic investigations consistently showed reduced proliferation/viability, increased apoptosis, and decreased migration/invasion following NF-κB-modulatory interventions; one genetic investigation implicated miR-9 in NF-κB1-dependent invasive programs. Human tissue investigations revealed NF-κB family expression with HLA upregulation and immune infiltration, more so in monosomy of chromosome-3/BAP1-negative tumors. There was variable reporting of concentrations and time courses, and cell-line authentication and numeric effect sizes were variably present. Table 2 presents the complete study-level data extraction, including all extracted fields, available effect estimates, and comments on missing data.

Evidence of activation

In tumors of patients and in UM model systems, the strongest direct evidence for canonical NF-κB activation is from research on UM cells with constitutive nuclear RelA (p65) location lowered with pathway suppression, and suppression of TNFα-induced NF-κB activation in UM cells, consistent with IKKβ/IκBα/RelA (p65)/p50 signaling [4, 5]. In metastases, multiple series report elevated levels of NF-κB family members (NF-κB1, RelA (p65), and noncanonical NF-κB2, RelB, NIK)

with higher NF-κB2, RelB, and NIK correlating with an HLA-high, leukocyte-infiltrated phenotype and with loss of BAP1, in keeping with noncanonical (NIK/IKKα/p100→p52/RelB) axis involvement—this despite most tumor studies being correlative, not kinetic/functional, for p100→p52 processing [3, 6, 19, 20]. NF-κB activity evidence in immune/stromal compartments is indirect, from cytokine-rich aqueous humor and leukocyte penetration associated with antigen-presentation programs; direct branch-specific readouts in non-tumor cells are limited in this corpus [18, 20, 21] (Table 3).

Canonical NF-κB activation in UM tumor cells is confirmed by human UM cell line experiments that show constitutive NF-κB activity with nuclear RelA (p65) suppressed by the inhibitor BAY11-7082, along with apoptosis induction and blocked migration—a direct readout of activation within the tumor cell compartment [5]. Another canonical evidence consists of TNFα stimulation assays in UM cells in which niclosamide blocked NF-κB activation, as expected again with IKKβ/IκBα/RelA (p65)/p50 signaling initiated by a canonical cytokine stimulus [4]. Further investigation defined NF-κB family member expression in primary and metastatic UM (NF-κB1, NF-κB2, RelA [p65], RelB, NIK) using immunofluorescence, western blot analysis, and quantitative polymerase chain reaction (qPCR). The results report presence and relative abundance, with increased NF-κB2, RelB, and NIK mRNA in metastases, but provide minimal direct activation kinetics [3]. Clinical series uncovered canonical NF-κB in UM and constitutive c-REL expression with correlation to prognosis, further illustrating the importance of REL family activity in human cancer [9, 10].

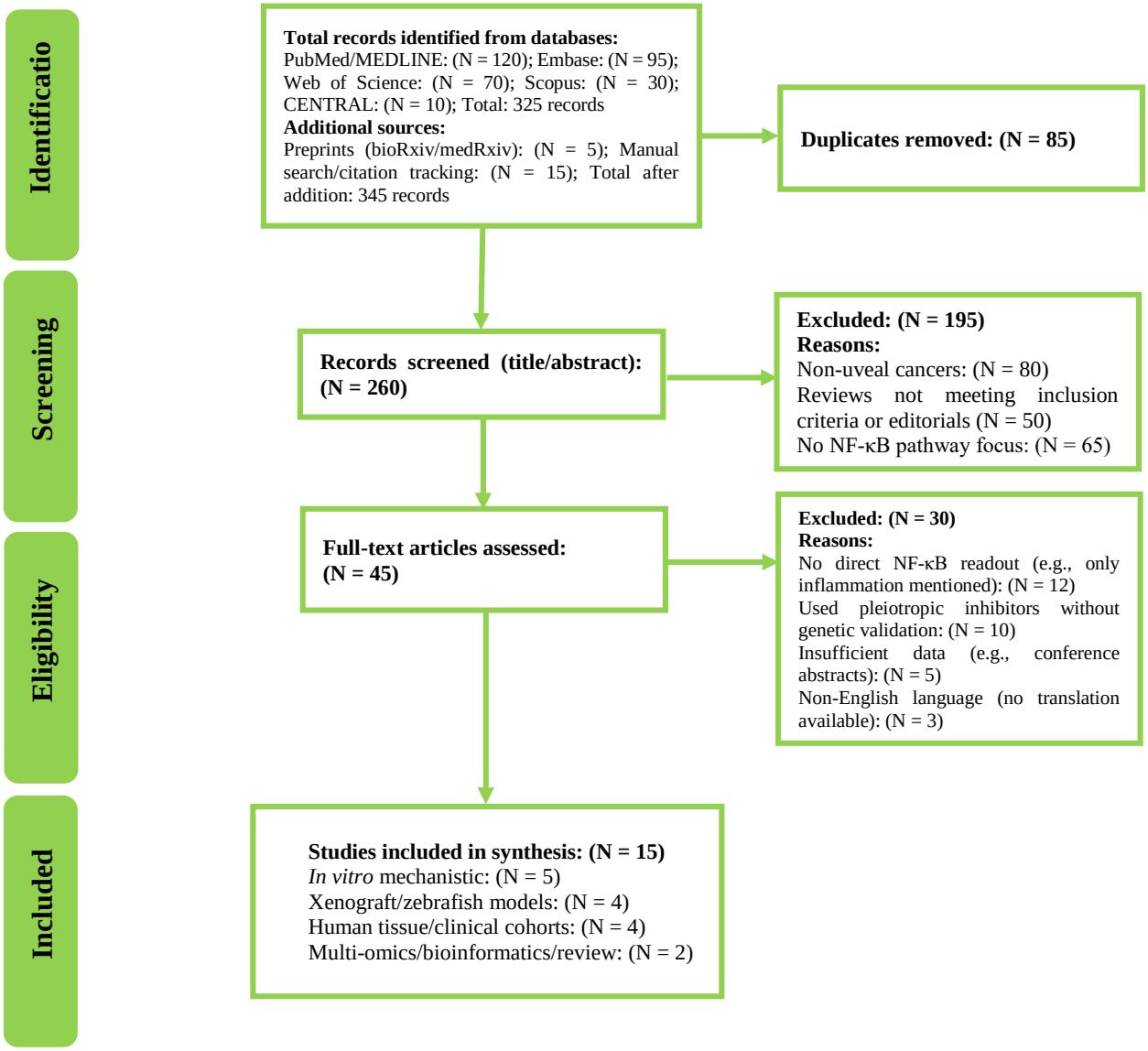

Figure 1. PRISMA flow diagram of study selection. Abbreviations: N, number of records; CENTRAL, Cochrane Central Register of Controlled Trials; NF-κB, nuclear factor kappa-B; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses.

Table 2. Data extraction of 15 included studies

Author (Year)	Design/type	UM models/ provenance (genetics/BAP1)	Inputs/perturbation (stimuli, agents, genetic)	Direct NF-κB readouts (assay; time; branch)	Downstream outputs	*In vivo* endpoints	Statistics (reported)	Effect estimates (summary)	Fund /COI
Ouyang et al. 2024) [29]	Multi-omics; *in vitro*; *in vivo* growth/metastasis; Hepatic stellate cell activation.	*Gαq*-mutant UM cells; hepatic stellate cells; *in vivo* models.	Target neural growth factor-inducible gene (VGF) genetically/pharmacologically; assess MAPK/CREB; combine Gαq + MEK inhibition.	No direct NF-κB readouts.	Tumor growth; stellate cell fibrosis activation; secretome.	Reduced tumor burden with combined inhibition (numbers NR).	NR	Directional suppression of growth; paracrine loop evidence.	NR
Zhang et al. (2023) [24]	Bioinformatics (TCGA and cBioPortal databases) + *in vitro* perturbation/rescue.	Public UM cohorts; UM cell lines (NR).	Manipulate BAP1; NF-κB overexpression (rescue).	NF-κB activity inferred by GSEA; experimental: BAP1 mutations inhibit NF-κB (assay NR).	Macrophage cytokine secretion/antigen presentation; immune infiltration estimates.	NA	GSEA; survival analyses (details NR).	BAP1 mutations ↓ NF-κB signaling; NF-κB overexpression reverses macrophage-related effects.	NR
Sundaramurthi et al. (2023) [16]	*In vitro* viability/proteomics; zebrafish xenograft.	OMM2.5 metastatic UM cell line; zebrafish larvae.	Ergolide (sesquiterpene lactone).	None; NF-κB relevance inferred (not tested).	Long-term proliferation; whole-cell/extracellular vesicle proteomes.	Zebrafish xenograft burden reduced.	Group comparison ;proteomics stats NR.	*In vitro* survival ↓ 48.5–99.9% (significant); zebrafish burden ↓ 56% (significant).	NR
Lapadula and Benovic, (2021) [1]	Narrative review on GNAQ/GNA11 oncogenic activation.	NA	NA	NA	NA	NA	NA	NA	NA
Singh et al. (2020) [10] **(abstract)**	Human observational.	Patient tumors (n NR).	NA	c-REL expression (assay NR); canonical-related.	Clinicopathologcorrelations; outcomes.	NA	NR	Directional association claimed; details NR.	NR
Singh et al. (2019) [9] **(abstract)**	Human observational.	Patient tumors (n NR).	NA	Canonical NF-κB identified (assay NR).	Outcome association (metrics NR).	NA	NR	Directional association claimed; details NR.	NR
Souri et al. (2019) [19]	Human observational cohort (n = 64).	Primary UM; monosomy of chromosome-3/BAP1 status annotated.	NA (observational)	Microarray expression of NF-κB1, NF-κB2, RelB; branch: noncanonical signal enriched.	HLA class I IHC; T-cell/macrophage infiltration.	NA	Correlation analyses; details NR.	NF-κB components positively correlate with HLA and infiltrates; enriched in monosomy of chromosome-3/BAP1-negative tumors.	NR
Zhou et al. (2017) [4]	*In vitro* + mouse xenograft.	UM cell lines (NR); xenografts (strain NR).	Niclosamide, p-niclosamide; TNFα; N-acetylcysteine; MMP-9 shRNA.	TNFα-induced NF-κB activation blocked (assay NR); branch: canonical.	Viability/proliferation; apoptosis; migration/invasion; ROS.	p-Niclosamide reduced tumor burden (magnitude NR).	NR	Directional: ↓ proliferation/ ↓ migration/ ↓ invasion; ↑ apoptosis; NAC partially rescues apoptosis.	NR
van Essen et al. (2016) [20]	Human observational (28 enucleated UM) with arrays/IHC; xenograft comparison.	Primary UM; matched xenografts in SCID mice.	NA	NF-κB not directly assayed.	HLA class I and II; TAP1; leukocyte infiltration; association with monosomy of chromosome-3.	Non-interventional xenograft expression comparison.	NR	↑ HLA with infiltrates; links to monosomy of chromosome-3.	NR
Bronkhorst and Jager (2013) [18]	Narrative review on inflammation in UM.	NA	NA	NA	NA	NA	NA	NA	NA

Hu et al. (2012) [5]	*In vitro* + mouse xenograft.	Human UM lines (NR); xenograft (details NR).	BAY11-7082; dose-response.	↓ nuclear RelA (p65) by immunofluorescence/ fractionation (modality implied); branch: canonical.	↑ caspase-3; ↓ anti-apoptotic protein Bcl-2; proliferation and migration reduced.	Xenograft growth inhibition (no numbers).	NR	Dose dependent apoptosis and growth inhibition; migration reduced.	NR
Liu et al. (2012) [14]	*In vitro* (microRNA [miRNA] mechanism).	UM cell lines with stratified invasiveness (details NR).	miR-9 mimic/inhibitor; NF-κB1 3′UTR luciferase.	Direct targeting of NF-κB1 (p105/p50); branch: canonical via NF-κB1.	Migration/invasion; MMP-2, MMP-9, and VEGFA expression.	NA	NR	↓migration/ invasion; ↓ MMP-2, MMP-9, and VEGFA upon miR-9; reporter confirms NF-κB1 targeting.	NR
Dror et al. (2010) [3]	Human tissues (primary UM n = 7; liver metastasis n=7) + *in vitro* pharmacology.	Patient tumors; UM liver metastasis-derived cell lines; drivers/BAP1 NR.	BMS-345541 (IκB kinase protein inhibitor); DHMEQ (RelA [p65]); doses/times NR.	Tumor qPCR, immunofluorescence, and western blot analysis: NF-κB1, NF-κB2, RelA (p65), RelB, NIK; *in vitro* inhibition inferred; branch: canonical + noncanonical.	Proliferation (MTT assay, methylene blue, Ki-67); apoptosis (cleaved caspase-3).	NA	Standard group comparison implied; details NR.	↓ proliferation; ↑ apoptosis with inhibitors; higher NF-κB2, RelB, and NIK mRNA in metastasis.	NR
Ly et al. (2010) [21]	Human cross-sectional cytokine profiling.	Aqueous humor from UM (n = 37) vs. cataract controls.	NA	None (NF-κB not directly assayed).	Elevated cytokines; MCP-3 associated with CD68+ macrophages; correlations with prognostic factors.	NA	NR	Directional elevations; numeric values NR.	NR
Meir et al. (2007) [6]	Human comparative transcriptomics (7 primary vs. 7 liver mets) with qPCR/IHC.	Patient tissues.	NA	NF-κB2 upregulated in mets; IHC protein validation; branch: noncanonical.	193 metastasis-associated genes; CDK4 validation.	NA	Microarray with false discovery rate; details NR.	NF-κB2 elevation in liver mets; metastasis program resembles liver.	NR

Abbreviations: UM, uveal melanoma; BAP1, BRCA1 associated protein-1; NF-κB, nuclear factor kappa-B; COI, conflict of interest; NR; not reported in available summaries; DHMEQ, Dehydroxymethylepoxyquinomicin an NF-κB inhibitor that blocks the nuclear translocation of NF-κB; qPCR, quantitative polymerase chain reaction; NIK, NF-κB-inducing kinase; MTT assay, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; NA, not applicable; TNFα, tumor necrosis factor α; MMP, matrix metalloproteinase; ROS, reactive oxygen species; NAC, N-acetylcysteine; BAY11-7082, a specific NF-κB inhibitor; n, numbers; IHC, immunohistochemical staining; HLA, human leukocyte antigen; 3′UTR, 3' untranslated regions; VEGFA, vascular endothelial growth factor A; GSEA, gene set enrichment analysis; c-REL, a member of the nuclear factor κB transcription factor family; MAPK, mitogen-activated protein kinase; CREB, cAMP response element binding protein; MEK, mitogen-activated protein kinase kinase; MCP, monocyte chemoattractant protein.

Table 3. Study-level evidence of NF-κB activation in uveal melanoma: branch, readouts, and compartments

Author (Year)	Patients/models	NF-κB branch implicated	Primary NF-κB readouts reported	Cellular compartment with evidence	Key findings relevant to activation	Evidence strength
Sundaramurthi et al. (2023) [16]	Metastatic UM line; zebrafish xenograft.	Unspecified (NF-κB-modulatory class).	Anti-UM effects; proteomic shifts (NF-κB-relevant nodes among others).	Tumor cells.	Small-molecule activity with plausible NF-κB relevance; not a direct activation study.	Indirect/ancillary.
Singh et al.(2020) [10]	Clinical series.	Canonical-related (c-REL).	Constitutive c-REL expression vs. clinicopathologic parameters; outcome associations.	Tumor tissues (bulk).	c-REL expression in UM relates to clinical features/outcome.	Component expression; no activation readout.
Souri et al. (2019) [19]	Primary UM cohort (n = 64).	Noncanonical emphasized; canonical components also.	Microarray expression of NF-κB family; correlation with HLA class I and infiltrating leukocytes; enrichment in monosomy of chromosome-3/BAP1-negative tumors.	Tumor tissues (bulk).	NF-κB component expression correlates with inflamed phenotype and adverse genetics; suggests NF-κB involvement in antigen presentation.	Correlative tumor data; no direct activation readouts.

Singh et al. (2019) [9]	Clinical series (details in abstract unavailable).	Canonical (reported).	Identification of canonical NF-κB pathway; association with outcome (specific assays not in abstract).	Tumor tissues (bulk).	Canonical NF-κB presence in UM with prognostic relevance.	Reported identification; readouts not specified.
Zhou et al. (2017) [4]	Human UM cell lines; xenograft model.	Canonical (TNFα-induced).	Abrogation of TNFα-induced NF-κB activation by niclosamide (assay type not specified in abstract).	Tumor cells.	TNFα stimulates NF-κB in UM cells; niclosamide blocks activation and suppresses malignant phenotypes.	Direct stimulus-response; readout unspecified (canonical inference from TNFα).
van Essen et al. (2016) [20]	Primary UM; matched xenografts.	Indirect (NF-κB-linked antigen presentation).	HLA class I and II expression and peptide-loading machinery; association with leukocyte infiltration and monosomy of chromosome-3 status.	Tumor tissues (bulk).	Inflamed UM shows high HLA/peptide-loading machinery expression; consistent with NF-κB-regulated antigen-presentation programs.	Indirect linkage; no NF-κB assay.
Bronkhorst and Jager (2013) [18]	Review on inflammation in UM.	Indirect.	Synthesis of cytokines/immune context.	Not applicable.	Context for NF-κB-driven inflammatory programs in UM.	Background synthesis.
Hu et al. (2012) [5]	Human UM cell lines; xenografts.	Canonical (IKKβ/IκBα/RelA (p65)/p50).	Decrease in RelA (p65) nuclear translocation after BAY11-7082; constitutive NF-κB activity described.	Tumor cells.	Constitutive NF-κB activation in UM cells. BAY11-7082 reduces nuclear RelA (p65), induces apoptosis, inhibits migration of UM cells and xenograft growth.	Direct activation readout in tumor cells.
Liu et al. (2012) [14]	UM cell lines (invasiveness stratified).	Canonical-related (via NF-κB1/p50).	miR-9 directly targets NF-κB1 3′UTR; modulation of NF-κB targets (MMP-2, MMP-9, and VEGFA).	Tumor cells.	Genetic control of NF-κB1 influences invasion and target gene expression.	Mechanistic link to NF-κB1; activation status not directly assayed.
Dror et al. (2010) [3]	Primary UM (n = 7) and liver metastases (n = 7); UM metastasis-derived lines.	Noncanonical suggested; canonical present.	qPCR, immunofluorescence, western blot analysis for NF-κB family (NF-κB1, NF-κB2, RelA (p65), RelB, NIK); higher NF-κB2, RelB, and NIK mRNA in metastases; inhibitor responses (BMS-345541, DHMEQ).	Tumor tissues (bulk); tumor cells (lines).	Presence of canonical and noncanonical components; noncanonical components enriched in metastases; pathway inhibition reduces proliferation/increases apoptosis.	Component expression and pharmacologic sensitivity; limited direct activation kinetics.
Ly et al. (2010) [21]	Aqueous humor from UM eyes vs. cataract controls.	Indirect (canonical cues).	Multiplex cytokines; association with CD68+ macrophages.	Ocular microenvironment; infiltrates.	Cytokine-rich milieu (e.g., MCP-3) associated with macrophages; compatible with canonical NF-κB activation.	Microenvironmental context; no NF-κB assay.
Meir et al. (2007) [6]	Primary UM vs. liver metastases (transcriptomics; IHC).	Noncanonical suggested.	Microarray showing NF-κB2 upregulation in metastases; IHC validation of NF-κB2 protein.	Tumor tissues (bulk).	NF-κB2 increased in metastases; supports noncanonical pathway involvement in advanced disease.	Component abundance; no activation kinetics.

Abbreviations: NF-κB, nuclear factor kappa-B; UM, uveal melanoma; IKK, inhibitory kappa B kinases; IκBα, a regulatory IκB protein in the cytoplasm to restrict NF-κB activation; BAY11-7082, a specific NF-κB inhibitor; TNFα, tumor necrosis factor α; qPCR, quantitative polymerase chain sreaction; NIK, NF-κB-inducing kinase; BMS-345541, IκB kinase protein inhibitor; DHMEQ, Dehydroxymethylepoxyquinomicin an NF-κB inhibitor that blocks the nuclear translocation of NF-κB; IHC, immunohistochemical staining; n, numbers; HLA, human leukocyte antigen; BAP1, BRCA1 associated protein-1; c-REL, a member of the nuclear factor κB transcription factor family; MCP, monocyte chemoattractant protein; miR-9, microRNA 9; 3′UTR, 3' untranslated regions; MMP, matrix metalloproteinase; VEGFA, vascular endothelial growth factor A.

Table 4. Functional dependence of uveal melanoma phenotypes on NF-κB signaling.

Author (Year)	Perturbation (pathway focus)	NF-κB readout paired with phenotype	Phenotypes assessed	Key results on dependence	*In vivo* outcome	Notes/limitations
Souri et al. (2019) [19]	None (observational tumor cohort).	Higher NF-κB1/NF-κB2/RelB expression associated with HLA class I and immune infiltrates.	Antigen presentation (HLA I), immune infiltration.	Correlations suggest NF-κB involvement in HLA/inflammatory programs, especially in BAP1-negative tumors.	NA	No perturbation; cannot ascribe functional dependence.
Zhou et al. (2017) [4]	Niclosamide/p-niclosamide (blocks TNFα-induced NF-κB activation; canonical).	Abrogation of TNFα-induced NF-κB activation in UM cells.	Proliferation/viability, apoptosis, migration/invasion.	Blocking canonical activation decreased proliferation, increased apoptosis, and reduced migration/invasion. ROS quenching by N-acetylcysteine-attenuated apoptosis.	p-Niclosamide reduced xenograft tumor burden.	Readout method not specified in abstract; multi-target drug but clear TNFα→NF-κB blockade is shown.
van Essen et al. (2016) [20]	None (tumor and xenograft comparison).	HLA class I and II and peptide-loading machinery vs. leukocyte infiltration.	Antigen presentation.	Inflamed tumors show high HLA and peptide-loading machinery; consistent with NF-κB-regulated programs.	NA	No NF-κB perturbation; dependence not established.
Hu et al. (2012) [5]	BAY11-7082 (IκBα phosphorylation blocker; canonical).	Reduced RelA (p65) nuclear translocation in UM cells.	Proliferation/viability, apoptosis (caspase-3), migration.	Canonical NF-κB inhibition induced apoptosis and reduced proliferation and migration, indicating dependence of survival and motility on NF-κB activity.	Xenograft growth inhibited.	BAY11-7082 has pleiotropic effects, but nuclear RelA (p65) localization and its reversal by treatment support pathway specificity.
Liu et al. (2012) [14]	miR-9 overexpression/knockdown (directly targets NF-κB1/p105/p50).	Direct repression of NF-κB1; modulation of known NF-κB targets (MMP-2, MMP-9, and VEGFA).	Migration/invasion; target gene expression.	Genetic suppression of NF-κB1 decreased invasion and downregulated NF-κB effector genes, indicating dependence of invasive phenotype on NF-κB1.	NR	Activation status (e.g., RelA [p65]/RelB localization) not assayed; nevertheless, direct genetic hit on NF-κB1 provides strong mechanistic linkage.
Dror et al. (2010) [3]	BMS-345541 (IKKβ inhibitor) and DHMEQ (RelA [p65] inhibitor).	NF-κB family expression characterized; inhibitor effects tested.	Proliferation (MTT assay/methylene blue), Ki-67, apoptosis (caspase-3).	IKKβ/RelA (p65) targeting reduced proliferation and increased apoptosis in UM metastasis-derived lines, supporting NF-κB dependence of survival.	NR	Abstract does not state a paired activation readout during perturbation; pathway specificity inferred from targets.
Ly et al. (2010) [21]	None (aqueous humor cytokines).	Cytokine milieu associated with macrophages.	Cytokine/chemokine programs.	Elevated cytokines in UM eyes; supports a context that can engage NF-κB.	NA	No tumor-cell NF-κB perturbation/readout.
Meir et al. (2007) [6]	None (primary vs. liver metastasis profiling).	NF-κB2 upregulation with IHC validation in metastases.	Association with metastatic state.	Noncanonical components elevated in metastases, implying potential role in progression.	NA	No functional test; no direct readout of p100→p52.

Abbreviations: NF-κB, nuclear factor kappa-B; BAY11-7082, a specific NF-κB inhibitor; UM, uveal melanoma; TNFα, tumor necrosis factor α; ROS, reactive oxygen species; BMS-345541, IκB kinase protein inhibitor; IKK, inhibitory kappa B kinases; DHMEQ, Dehydroxymethylepoxyquinomicin an NF-κB inhibitor that blocks the nuclear translocation of NF-κB; MTT assay, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; miR-9, microRNA-9; MMP, matrix metalloproteinase; VEGFA, vascular endothelial growth factor A; HLA, human leukocyte antigen; BAP1, BRCA1 associated protein-1; IHC, immunohistochemical staining.

Table 5. Genetic and microenvironmental modulators of NF-κB signaling in uveal melanoma.

Author (Year)	Alteration or cue	Model or patient context	NF-κB branch implicated	NF-κB readout type	Reported outputs/modulation	Compartment specificity	Reciprocity with immune/stroma	Evidence type/strength
Ouyang et al. (2024) [29]	Hepatic stellate cell activation (VGF loops).	Gαq-mutant UM; multi-omics and *in vivo*.	NF-κB not directly assayed.	Secretome/transcriptome; HSCs activation readouts.	UM-derived VGF promotes HSCs fibrosis and metastatic colonization.	Tumor cell secreted factor; hepatic stroma.	Clear tumor-stroma reciprocity in liver niche; NF-κB role not directly tested.	Experimental; NF-κB linkage is inferential.
Zhang et al. (2023) [24]	BAP1 mutation (contrasting report).	Bioinformatic + cell-based analyses.	NF-κB reported as inhibited by BAP1 mutation.	Pathway activity inferred; rescue by NF-κB overexpression.	Decreased macrophage cytokine secretion/antigen presentation; effects reversed by NF-κB reconstitution.	Myeloid/macrophage functions highlighted; tumor cell context also analyzed.	Suggests BAP1-dependent dampening of NF-κB shaping an immunosuppressive milieu.	Mixed computational/experimental; contrasts with [4].
Lapadula and Benovic (2021) [1]	GNAQ/GNA11 oncogenic activation.	UM biology review; pathway synthesis.	Canonical/noncanonical potential via upstream crosstalk.	Mechanistic review synthesis.	$G\alpha_{q/11}$→PKC/MAPK pathways that interface with NF-κB signaling; therapeutic implications.	Tumor cell-intrinsic.	Upstream oncogenic input may tune NF-κB outputs.	Review; not a direct activation study.
Souri et al. (2019) [19]	Monosomy of chromosome-3/BAP1-negative status.	Cohort of 64 primary UM.	Noncanonical emphasized (NF-κB2, RelB up), canonical components present.	Tumor microarray expression; correlations.	Higher NF-κB family expression correlates with HLA class I and T-cell/macrophage infiltration; inflamed phenotype.	Bulk tumor (tumor cells plus infiltrates).	Links tumor genetics to immune infiltration and antigen presentation.	Observational, strong correlations; no activation kinetics.
Zhou et al. (2017) [4]	TNFα stimulation.	UM cell lines; xenograft.	Canonical (IKKβ/IκBα/RelA (p65)/p50).	TNFα-induced NF-κB activation blocked by niclosamide.	Decreased proliferation, increased apoptosis; reduced migration/invasion upon blockade.	Tumor cells (*in vitro*); *in vivo* antitumor effect of p-niclosamide.	Cytokine cue from microenvironment engages tumor NF-κB.	Experimental; direct stimulus-response.
van Essen et al. (2016) [20]	Leukocyte infiltration in tumors.	Primary UM and matched xenografts.	Indirect link to NF-κB programs.	HLA class I and II and peptide-loading machinery vs. infiltrates.	Inflamed tumors show high HLA/peptide-loading machinery expression; associated with monosomy of chromosome-3 status.	Tumor tissue (bulk).	Infiltrates associate with antigen-presentation programs in tumor.	Observational; no NF-κB perturbation.
Ly et al. (2010) [21]	Cytokine-rich microenvironment in UM aqueous humor.	Aqueous humor from UM eyes vs. cataract controls.	Indirect canonical cues.	Multiplex cytokine profiling; macrophage IHC.	Higher cytokines (e.g., MCP-3) correlate with CD68+ macrophages.	Ocular microenvironment; infiltrates.	Provides upstream signals that can activate NF-κB in tumor and myeloid cells.	Observational; no NF-κB readout.
Dror et al. (2010) [3]	Metastatic enrichment of NF-κB2, RelB, and NIK.	Primary vs. metastatic UM; UM cell/tissue series.	Noncanonical emphasized.	qPCR, immunofluorescence, and western blot analysis; expression comparisons.	Higher NF-κB2, RelB, and NIK in metastases; presence of NF-κB1/RelA (p65) as well.	Tumor tissues; UM cell lines.	Suggests shift toward noncanonical signaling with progression.	Descriptive expression; limited functional linkage.
Meir et al. (2007) [6]	Liver metastasis context.	Primary UM vs. liver metastases.	Noncanonical suggested (NF-κB2 up).	Microarray with IHC validation (NF-κB2 protein).	NF-κB2 increased in metastases; aligns with advanced disease.	Tumor tissue (metastases).	Implies adaptation to hepatic niche; branch-specific activation not directly shown.	Observational with protein validation.

Abbreviations; NF-κB, nuclear factor kappa-B; BAP1, BRCA1 associated protein-1; UM, uveal melanoma; HLA, human leukocyte antigen; PKC, protein kinase C; MAPK, mitogen-activated protein kinase; TNFα, tumor necrosis factor α; IKK, inhibitory kappa B kinases; IκBα, a regulatory IκB protein in the cytoplasm to restrict NF-κB activation; IHC, immunohistochemical staining; MCP, monocyte chemoattractant protein; NIK, NF-κB-inducing kinase; qPCR, quantitative polymerase chain reaction; VGF, neural growth factor-inducible gene; HSC, hepatic stellate cells.

Table 6. Therapeutic modulation of NF-κB signaling in uveal melanoma models

Author (Year)	Intervention (class)	Intended NF-κB node or linkage	On-target NF-κB readout shown	Tumor-cell phenotypes (*in vitro*)	*In vivo* outcome	Magnitude/consistency highlights	Key caveats
Sundaramurthi et al. (2023) [16]	Ergolide (pharmacologic; sesquiterpene lactone).	NF-κB-modulatory class (not isolated here).	Not centered on NF-κB readouts.	Large, dose-dependent ↓ viability (48.5–99.9%).	-56% zebrafish xenograft fluorescence.	Strong magnitude of antitumor effect.	NF-κB on-target engagement not demonstrated; mechanism broader.
Lapadula and Benovic (2021) [1]	Upstream $G\alpha_{q/11}$-targeted strategies; PKC/MEK modulation (conceptual).	Inputs that converge on NF-κB.	NA (review synthesis).	Mechanistic rationale for NF-κB damping via upstream blockade.	NA	Provides framework for combinations with NF-κB-directed agents.	No primary UM data with NF-κB readouts in this set.
Zhou et al. (2017) [4]	Niclosamide; p-niclosamide (pharmacologic/repurposed).	Blocks TNFα-induced NF-κB activation (canonical); elevates ROS.	TNFα→NF-κB activation abrogated (assay not specified in abstract).	↓ proliferation/viability; ↑ apoptosis (partly ROS-dependent); ↓ migration/invasion.	p-Niclosamide reduced tumor burden in xenograft.	Robust multi-phenotype inhibition aligned with blocked canonical activation.	Polypharmacology; NF-κB readout method not detailed.
Hu et al. (2012) [5]	BAY11-7082 (pharmacologic).	IκBα phosphorylation blocker (canonical).	↓ RelA (p65) nuclear translocation in UM cells.	↓ proliferation/viability; ↑ apoptosis (caspase-3↑); ↓ migration.	↓ xenograft growth.	Consistent suppression of survival and motility with direct canonical readout.	Pleiotropic compound; no genetic rescue.
Liu et al. (2012) [14]	miR-9 overexpression/knockdown (genetic).	Direct targeting of NF-κB1 (p105/p50).	Direct 3′UTR targeting of NF-κB2; concordant ↓ of NF-κB targets (MMP-2, MMP-9, and VEGFA).	↓ invasion/migration; modulation of target gene expression.	NR	Genetic evidence that NF-κB1 supports invasive program.	Did not assay RelA (p65)/RelB localization; focuses on motility rather than survival.
Dror et al. (2010) [3]	BMS-345541 (IKKβ inhibitor) (pharmacologic).	IKKβ (canonical).	NF-κB component expression profiled; concurrent inhibition readout not specified.	↓ proliferation (MTT assay/methylene blue; Ki-67↓); ↑ apoptosis (caspase-3↑).	NR	Effects consistent with canonical pathway dependence.	Lack of paired pathway readout in abstract; off-target risk lower than older inhibitors but still present.
Dror et al. (2010) [3]	DHMEQ (pharmacologic).	RelA (p65) nuclear import/function (canonical).	Not detailed in abstract.	↓ proliferation; ↑ apoptosis in metastatic UM-derived lines.	NR	Aligns with canonical dependence across lines tested.	On-target confirmation during treatment not shown in abstract.

Abbreviations: NF-κB, nuclear factor kappa-B; BAY11-7082, a specific NF-κB inhibitor; IκBα, a regulatory IκB protein in the cytoplasm to restrict NF-κB activation; UM, uveal melanoma; TNFα, tumor necrosis factor α; ROS, reactive oxygen species; BMS-345541, IκB kinase protein inhibitor; IKK, inhibitory kappa B kinases; MTT assay, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; DHMEQ, Dehydroxymethylepoxyquinomicin an NF-κB inhibitor that blocks the nuclear translocation of NF-κB; miR-9, micoRNA-9; 3′UTR, 3' untranslated regions; MMP, matrix metalloproteinase; VEGFA, vascular endothelial growth factor A; PKC, protein kinase C; MEK, mitogen-activated protein kinase kinase.

Noncanonical NF-κB activation is supported by overexpression of NF-κB2 (verified at the protein level) in liver metastases vs. primaries and elevated NF-κB2, RelB, and NIK expression in metastatic and BAP1-negative tumors; these trends are correlated with an HLA-high, leukocyte-rich primary UM inflamed phenotype [3, 6, 19, 20]. Though these findings are suggestive, most studies did not directly measure key markers of noncanonical NF-κB activation, such as p100 processing to p52 or RelB nuclear translocation; the evidence should therefore be viewed as indirect rather than definitive.

Regarding compartments, direct branch-aware readouts are strongest in UM cells lines [4, 5]. In patient tissues, NF-κB component expression and HLA/infiltration correlations are measured in bulk tumor sections and hence reflect tumor cells with inputs from infiltrates; specific nuclear localization of Rel subunits by cell type is not generally seen in abstracts [3, 6, 19, 20]. Microenvironmental stimulation is indirectly supported by elevated aqueous humor cytokines that are associated with macrophage infiltration and which would be expected to stimulate canonical NF-κB in both tumor and myeloid cells, but branch-specific stromal/immune cell readouts are not described directly [18, 20, 21].

These papers have evidence for active canonical NF-κB in UM tumor cells that points to noncanonical regulators in later-stage, inflamed disease states in patients; it also pinpoints gaps—particularly the absence of p100→p52 kinetics, RelB nuclear localizations, κB-reporters, EMSA/ChIP, and cell type-resolved assays within tumor microenvironments—that need to be addressed by future research (Table 3).

Functional dependency and phenotypes

In the included papers, canonical NF-κB signaling shares consistent functional importance to UM cell proliferation and motility: pharmacologic blockade reducing NF κB function (RelA [p65] nuclear translocation or TNFα induced activation) decreases proliferation/viability, induces apoptosis, and suppresses migration/invasion; two of the studies also show *in vivo* growth inhibition in xenograft models [4, 5]. Genetic suppression of the pathway by miR-9 (straight inhibition of NF-κB1/p50) diminishes invasion and lowers NF-κB target genes (*MMP-2*, *MMP-9*, and *VEGFA*), showing a tumor-intrinsic need for invasive programs [14]. Additional inhibitor data (IKKβ and RelA [p65] inhibition) are in agreement with these observations on survival/apoptosis in UM cell lines, although straight NF-κB measurements were less certain in the abstract [3]. Conversely, for cytokine/chemokine and antigen presentation (HLA class I and II, peptide-loading complex) programs, current evidence in patients is correlative—linking enhanced NF-κB component expression to HLA-high, leukocyte-rich tumors with metastasis—but lacking any direct perturbation-readout experiments proving NF-κB causality in such outputs in UM tissues [3, 6, 19–21]. Noncanonical branch activation (NF-κB2, RelB, and NIK) is strongly suggested by metastasis and BAP1-negative tumor expression patterns but lacks direct functional tests (e.g., p100→p52 processing, RelB nuclear translocation) associated with phenotype in this corpus [3, 6, 19, 20]. In general, the most apparent functional dependence lies on tumor cell proliferation/survival and invasion/migration through canonical NF-κB; *in vivo*, pathway inhibition reduces xenograft growth, but firm associations to antigen presentation, cytokine programs, and metastasis remain to be demonstrated using branch-aware, perturbation-based assays (Table 4).

Genetic and microenvironmental modulators

Together, UM genetics and the tumor microenvironment control NF-κB in branch- and compartment-specific ways. Monosomy of chromosome-3/BAP1 negative primary tumors evidences overexpression of NF-κB components—most prominently the noncanonical axis (NF-κB2/RelB)—that is linked with an HLA-high, leukocyte-rich inflamed phenotype, suggesting noncanonical involvement in adverse biology [19]. In contrast, a separate study reports that BAP1 mutations inhibit NF-κB signaling and reshape macrophage cytokine/antigen presentation programs, with NF-κB reconstitution restoring some effects—highlighting unresolved, context-dependent (tumor vs. myeloid) regulation [24]. Canonical NF-κB is directly activated in UM cells by TNFα and is pharmacologically targetable (e.g., niclosamide), linking inflammatory cytokines to tumor-intrinsic NF-κB outputs on survival and motility [4]. Clinically, leukocyte infiltration in UM is coupled with tumors upregulating HLA class I and II and peptide-loading machinery, consistent with NF-κB-associated antigen presentation programs imprinted by the microenvironment [20]. The aqueous humor of UM eyes contains elevated cytokines related to macrophage infiltration that provide upstream signals for canonical activation in both the tumor and the myeloid compartments [18, 21]. At the metastatic site, NF-κB2 is increased in liver metastases vs. primaries and NF-κB2, RelB, and NIK are increased in metastatic samples, supporting noncanonical involvement in hepatic colonization; still, direct p100→p52 processing or nuclear translocation of RelB has not been demonstrated in patient tissues here [3, 6]. Oncogenic $G\alpha_{q/11}$ signaling, the principal driver in UM, intersects with pathways upstream of NF-κB2 (e.g., PKC/MAPK) and instigates paracrine programs that precondition the hepatic niche (e.g., the neurosecretory protein VGF-mediated activation of hepatic stellate cells), implicating potential crosstalk with NF-κB2-regulated inflammatory readouts [1, 29]. Immediate NF-κB readouts in these stromal interactions are lacking in this work though [29] (Table 5).

Therapeutic modulation

Across the papers, pharmacologic blockade of canonical NF-κB (IKKβ/IκBα/RelA (p65)/p50) reproducibly inhibits *in vitro* UM malignant phenotypes directly, and in two cases prevents xenograft growth *in vivo*. BAY11-7082 inhibited RelA (p65) nuclear translocation and caused apoptosis with inhibition of migration and xenograft growth, showing on-target canonical pathway inhibition with resultant phenotype [5]. Niclosamide inhibited TNFα-induced NF-κB activation in UM cells and reduced proliferation, invasion/migration, and xenograft burden (with p-niclosamide), implying the cytokine-mediated canonical pathway is of functional relevance; apoptosis was moderately ROS-dependent [4]. IKKβ suppression (BMS-345541) or RelA (p65) nuclear function (DHMEQ) inhibited proliferation and increased apoptosis in metastatic UM-derived cell lines, as would be anticipated with canonical NF-κB reliance, although the particular concurrent pathway readouts are not defined in the abstract [3]. Genetic downregulation by miR-9 directly targeting NF-κB1 (p105/p50) inhibited invasion and downregulated NF-κB effector genes (*MMP-2*, *MMP-9*, and *VEGFA*), which is in accordance with a tumor-intrinsic role for NF-κB1 in motility programs [14]. One of the sesquiterpene lactones, ergolide, elicited extensive, dose-dependent reduction in metastatic UM cell viability (48.5–99.9%) and reduced zebrafish xenograft burden (-56%), but NF-κB on-target repression was not unique so pathway selectivity is uncertain [16]. Upstream $G\alpha_{q/11}$-targeted strategies and PKC/MRK

modulation are mechanistically linked to NF-κB in UM conceptually, but here in this corpus they are dealt with mainly by a review rather than branch-resolved readouts in UM models [1]. Overall, proliferation/survival and invasion/migration effect size is the same for canonical NF-κB-targeted perturbations; strict genetic knockdown/rescue of RelA (p65), IKKβ, RelB, NIK, and noncanonical specific antagonists were not seen in the initial studies on the list, with resultant gaps for pathway-specific causality and for antigen presentation/cytokine outputs *in vivo* [1, 3–5, 14, 16, 19] (Table 6).

DISCUSSION

In clinical samples and animal models of UM, the overall evidence is for activation of canonical and noncanonical NF-κB signaling, mechanistic evidence for the canonical pathway more robust in cell culture, and correlative evidence more robust in clinical samples for the noncanonical pathway.

Early tumor studies reported the expression of canonical members (NF-κB1, RelA [p65]) and noncanonical members (NF-κB2, RelB, NIK) in metastatic and primary tumors, with some of these transcripts more numerous in metastases, which verified the existence of both pathways within the disease process [3]. At the level of the functional readout, UM cells display constitutive canonical activity in that pharmacologic inhibition decreases nuclear RelA (p65) and TNFα further activates this pathway *in vitro*, indicating preserved responsiveness of the IKKβ/IκBα/RelA (p65) module to inflammatory inputs [4, 5]. In addition to these model systems, clinical series have shown canonical NF-κB pathway recognition and constitutive c-REL expression to be associated with clinicopathologic parameters, once more situating canonical-like Rel use in cancer, albeit with modest mechanistic perturbation in patient materials [9, 10].

The noncanonical pathway is directly implicated by tumor-level associations. Transcript and protein measurements indicate that NF-κB2 and RelB, along with NIK, are not only present but elevated in advanced contexts. NF-κB2 protein is overexpressed in liver metastases by immunohistochemistry, and primary-metastatic analyses show more NF-κB2, RelB, and NIK mRNA in metastases, as predicted from activation of the NIK/IKKα/p100→p52/RelB pathway in progression [3, 6]. In a different 64-tumor cohort, elevated NF-κB1, NF-κB2, and RelB expression correlated with increased levels of HLA class I and more T-cell/macrophage infiltration; these characteristics were overrepresented in monosomy of chromosome-3/BAP1-negative tumors which otherwise have a poor prognosis [19]. Combined, these results fit with a model of active canonical signaling in UM cells and cytokine-inducible, but preferentially inflammatory, high-risk tumor status and liver metastasis-associated noncanonical signaling. To that end, though, direct genetic manipulation of NIK, IKKα, and RelB in UM models is lacking in the current corpus, and branch assignment in tissues is derived from component expression instead of functional dependence, a flaw to be rectified in future studies [3, 19, 20].

Malignant phenotypes of UM have definite dependence on NF-κB signaling, specifically through the canonical axis. In metastatic UM cell lines, the IKKβ inhibitor BMS-345541 and the RelA (p65) nuclear import inhibitor DHMEQ inhibit proliferation and induce apoptosis, arguing for tonic canonical NF-κB being pro-survival [3]. BAY11-7082, inhibiting nuclear RelA (p65), triggers caspase-3-induced apoptosis and prevents proliferation and migration *in vitro* and xenograft growth *in vivo*, providing orthogonal confirmation with a second tool compound and an *in vivo* readout [5]. The anthelmintic niclosamide and its water-soluble prodrug suppress TNFα-induced NF-κB activation in UM cells, increase ROS, and suppress proliferation, migration, and invasion, with xenograft activity that emphasizes translational relevance; NAC-mediated rescue of apoptosis to some extent suggests that oxidative stress and NF-κB blockade are both responsible for the phenotype [4]. Genetic modulation confers specificity at the transcriptional terminus: miR-9 targets the 3′UTR of NF-κB1 (p105/p50) directly, suppressing migration/invasion and reducing the expression of established NF-κB targets (MMP-2, MMP-9, and VEGFA), thereby linking NF-κB transcriptional output to invasive and pro-angiogenic programs [14]. These studies define a crucial role for canonical NF-κB in UM cell survival and motility, with *in vivo* confirmation from xenograft experiments. Nonetheless, the majority of the small pharmacologic molecules used (e.g., BAY11-7082, niclosamide) are pleiotropic, and the field would be facilitated by pathway-specific, rescue-supported genetic manipulations of RelA (p65), IKKβ, NEMO, and, for completeness, NIK and RelB to define branch-specific requirements between phenotypes [3–5, 14].

Genetic environments and microenvironmental cues appear to regulate NF-κB branch activation and outcomes, yet directionality in some relationships is controversial. Transcriptomic correlation attributes monosomy of chromosome-3/BAP1-negative tumors to higher expression of NF-κB family members (specifically, NF-κB2/RelB) and higher HLA class I and leukocyte infiltration, attributing BAP1 loss to an inflamed, NF-κB-high state that would probably include noncanonical aspects [19]. Microenvironmental support is available: leukocytic infiltration is

associated with increased HLA class I and II and peptide-loading machinery, and aqueous humor from the eyes in UM is cytokine-enriched; these milieus are capable of initiating canonical activation and antigen-presentation programs within and surrounding the tumor [20, 21]. In contrast, a cellular and bioinformatic analysis has shown that mutations in BAP1 inhibit NF-κB signaling to reduce cytokine release and antigen presentation by macrophages. However, effects reversed by NF-κB reconstitution in rescue assays [24]. Such contradictory findings can be explained by differences in cellular compartment (tumor cell vs. myeloid), in which the NF-κB branch is dominant (canonical vs. noncanonical), or in the readouts, which necessitate BAP1-stratified, cell-type-specific, branch-resolved assays—ideally including RelA (p65) and RelB nuclear localization, IκBα and p100 processing kinetics, κB-reporters, and CRISPR (clustered regularly interspaced short palindromic repeats)-based perturbations—to close tumor-intrinsic vs. microenvironmental NF-κB regulation in UM [19–21, 24, 30–32].

The hepatic niche would likely intensify these dynamics. Liver metastases exhibit increased NF-κB2 and greater gene-expression resemblance with hepatic tissue, indicating niche adaptation and the potential for hepatic cytokines and stromal contacts to preserve NF-κB programs throughout colonization and outgrowth [10]. While the direct assays in which hepatic TNFα/IL-1β stimulate UM NF-κB-dependent survival *in vivo* were not performed in included papers, the overlap of cytokine-enriched microenvironments with established NF-κB-responsive UM cells renders this a plausible, testable hypothesis. More recent studies putting paracrine circuits and hepatic stellate cell activation at the epicenter of UM metastasis further reinforces the primacy of tumor-stroma communication, even if NF-κB is not assayed directly within those systems [29]. It is plausible to speculate, with appropriate caution, that these loops intersect with NF-κB-modulated cytokine and adhesion programs, especially considering the observed correlations between NF-κB family expression, HLA upregulation, and immune infiltration in high-risk tumors [19–21, 29, 31].

Therapeutically, there are a number of interventions that modulate NF-κB signaling in UM in a persistent, directionally concordant antitumor fashion, although magnitude and specificity vary. Agents acting proximally to the canonical pathway, DHMEQ and BMS-345541, are producing definitive reductions in proliferation and induction in metastatic UM lines apoptosis, confirming on-target inhibition of survival signaling [3]. BAY11-7082 also offers further evidence of pathway activation by reduced nuclear RelA (p65), as well as robust apoptosis induction, migration inhibition, and tumor inhibition *in vivo* [5]. Niclosamide and its soluble prodrug contribute to the portfolio with evidence of TNFα-induced NF-κB blockade, anti-proliferative and anti-invasive activity, and xenograft efficacy; partial ROS dependence of apoptosis is illustrative of polypharmacology that may be leveraged or circumvented in combination therapy [4]. Ergolide, a sesquiterpene lactone in a class usually reported to regulate NF-κB, reduces viability of metastatic UM cells and zebrafish xenograft burden, although NF-κB causality is not unique to that study [16]. Genetic reduction by miR-9 is a more specific hold on NF-κB1-driven invasive programs, adding pharmacology to transcript-level control [14]. These studies argue that NF-κB inhibition, most prominently the canonical IKKβ/RelA (p65) branch, systematically blocks UM survival and migration *in vitro* and reduces tumor burden *in vivo* in various models. Relatively less investigated are branch-specific pharmacotherapies for the noncanonical pathway (e.g., NIK or IKKα inhibitors) in UM and stringent genetic epistasis to demonstrate that observed effects of drugs are rescued by reexpression of targeted NF-κB branch.

Overall, UM has a dual-arm NF-κB profile where canonical signaling is easily seen and functionally linked to survival and motility, while noncanonical signaling defines inflammatory, high-risk disease and hepatic metastasis. The disease appears poised for NF-κB activation by both oncogenic signaling and cytokine-enriched microenvironments, yet causal, branch-resolved determinations, particularly in BAP1-defined settings and liver-tropic models, remain to be made. Follow-up studies that integrate correct pathway readouts with genetic manipulation in authentic UM models, such as metastasis assays, should clarify how niche signals and genetics skew NF-κB branch usage and what treatment modalities can most effectively and safely exploit this weakness [1, 3–5, 14, 19–21, 24, 29, 30].

There are a few limitations to this study. First, the study protocol was not registered in the PROSPERO database, which might affect transparency and restrict opportunities for eventual biases to be detected. Second, while a number of databases were searched, manual reference list-checking and gray literature (e.g., conference proceedings, dissertations) searches were not conducted systematically, which might exclude relevant unpublished data. Third, the inclusion of English-language articles only might lead to language bias. Moreover, pleiotropic inhibitors were employed in certain included studies without genetic validation, limiting definitive conclusions on NF-κB-specific effects. Heterogeneity of study design and NF-κB readout also precluded quantitative meta-analysis in some cases.

Finally, the absence of direct functional assays for noncanonical NF-κB signaling (i.e., p100→p52 processing) in clinical samples highlights a significant gap in the current evidence.

CONCLUSIONS

This review summarizes evidence implicating both canonical and noncanonical NF-κB signaling in UM progression, survival, and metastasis. While canonical NF-κB is mechanistically linked to tumor cell phenotypes, noncanonical signaling is linked to aggressive, immune-rich tumors. Further studies with branch-specific genetic manipulations and clinically relevant models are required to refine therapeutic targeting strategies.

ETHICAL DECLARATIONS

Ethical approval: Ethical approval was not required because the study involved analysis of already published data.

Conflict of interest: None.

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