Review

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Anti–TNF-α Signaling and Therapeutic Modulation in Intracranial Fusiform Aneurysms: A Systematic Review of Clinical and Translational Evidence

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Review

Anti–TNF-α Signaling and Therapeutic Modulation in Intracranial Fusiform Aneurysms: A Systematic Review of Clinical and Translational Evidence

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Abstract

Intracranial fusiform aneurysms represent a rare but clinically aggressive subtype of cerebrovascular disease, characterized by circumferential arterial dilation and a high risk of growth, ischemic complications, and rupture. Unlike saccular aneurysms, fusiform lesions lack well-established medical therapies to prevent progression or stabilize the aneurysm wall. Tumor necrosis factor–alpha (TNF-α) has emerged as a central mediator of aneurysm-associated inflammation and vascular remodeling, raising interest in TNF-α modulation as a potential therapeutic strategy. To systematically review and synthesize the available clinical and translational evidence evaluating TNF-α signaling and anti–TNF-α therapies in the context of intracranial fusiform aneurysms. A systematic literature search was conducted in PubMed/MEDLINE, Embase, and Google Scholar from database inception through February 2026 in accordance with PRISMA guidelines. Eligible studies included human, animal, and translational investigations examining TNF-α biology or anti–TNF-α interventions in relation to intracranial fusiform aneurysms, intracranial dolichoectasia, or vertebrobasilar dolichoectatic aneurysms. Study selection, deduplication, and screening were performed using Covidence systematic review software. Extracted outcomes included aneurysm growth, rupture, ischemic events, imaging characteristics, inflammatory signaling, and vascular remodeling. Given substantial heterogeneity in study design and outcome reporting, findings were synthesized narratively using structured evidence mapping. From 368 records identified, 14 studies met inclusion criteria following full-text review. Included studies encompassed preclinical models, translational mechanistic investigations, and limited clinical observational data. Across experimental models, TNF-α signaling was consistently associated with macrophage infiltration, matrix metalloproteinase activation, vascular smooth muscle cell phenotypic modulation, and aneurysm wall degeneration. TNF-α inhibition was associated with reduced aneurysm progression and rupture in preclinical settings, including when initiated after aneurysm formation. Clinical evidence remains limited but suggests a potential association between TNF-α modulation and aneurysm stability, although direct therapeutic data in intracranial fusiform aneurysm populations are sparse. Existing translational and preclinical evidence supports a contributory role for TNF-α–mediated inflammation in the progression of intracranial fusiform aneurysms and suggests that TNF-α inhibition may represent a promising disease-modifying strategy. However, clinical data remain insufficient to support routine therapeutic use. Prospective observational studies and early-phase clinical trials are needed to define the safety, timing, and efficacy of anti–TNF-α therapies in patients with intracranial fusiform aneurysms.

Keywords: tumor necrosis factor-alpha; anti–TNF therapy; intracranial fusiform aneurysm; vertebrobasilar dolichoectasia; inflammation; aneurysm progression; systematic review

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1. Introduction

Intracranial fusiform aneurysms are an uncommon but high-risk subtype of cerebrovascular disease, characterized by circumferential arterial dilation without a discrete aneurysmal neck. Unlike saccular aneurysms, which comprise approximately 90% of intracranial aneurysms, fusiform aneurysms are associated with a more aggressive natural history and limited therapeutic options. These lesions most frequently involve the vertebrobasilar circulation, where they present as vertebrobasilar dolichoectatic and fusiform aneurysms (VBDAs). Patients with VBDAs experience substantial morbidity and mortality related to aneurysm growth, ischemic stroke, and rupture.[1–3]

Observational studies have demonstrated poor outcomes in this population, with reported annual mortality rates ranging from 10% to 13%. Fusiform aneurysms exhibit annual growth rates of approximately 12%, rupture rates near 3%, and ischemic stroke rates approaching 6%.[2] In large multinational cohorts of patients with dolichoectatic vertebrobasilar aneurysms, a significant proportion of deaths have been directly attributed to aneurysm-related complications.[3] Transitional morphologies, which display features of both fusiform and dolichoectatic aneurysms, appear to carry the highest risk, with more than half progressing to aneurysm growth or rupture.[4] Established predictors of progression include aneurysm diameter greater than 7 mm, symptomatic presentation, mural thrombus, daughter sac formation, and mural T1 hyperintensity on magnetic resonance imaging.[4,5]

Despite advances in endovascular and microsurgical techniques, including flow diversion, stent-assisted coiling, and bypass procedures, treatment of intracranial fusiform aneurysms remains challenging. Deconstructive approaches are associated with higher complication rates than reconstructive strategies, and treatment-related mortality can exceed 10% even in contemporary series.[6–8] Importantly, no established medical therapies currently exist to prevent aneurysm formation, halt progression, or reduce rupture risk in patients with intracranial fusiform aneurysms, representing a significant unmet clinical need.

Current evidence implicates inflammatory pathways as central drivers of intracranial aneurysm pathogenesis. Tumor necrosis factor–alpha (TNF-α), a key proinflammatory cytokine, has been identified as a major mediator of aneurysm wall degeneration. TNF-α promotes macrophage infiltration, upregulation of matrix metalloproteinases (MMPs), vascular smooth muscle cell (VSMC) apoptosis, and extracellular matrix degradation.[9–11] In cerebral VSMCs, TNF-α induces a phenotypic switch from a contractile to a proinflammatory, matrix-remodeling state through transcriptional pathways involving Krüppel-like factor 4, resulting in increased expression of MMP-3, MMP-9, monocyte chemoattractant protein-1, and vascular cell adhesion molecule-1.[10] These changes contribute to progressive weakening of the arterial wall and aneurysm growth. Genetic and observational studies further support a causal association, demonstrating significantly elevated TNF-α expression in both ruptured and unruptured intracranial aneurysms compared with normal vessels.[9,11]

Anti–TNF-α therapies fall into two principal categories: biologic agents and small-molecule inhibitors. Biologic agents include monoclonal antibodies (infliximab, adalimumab, golimumab) and fusion proteins (etanercept, certolizumab pegol) that directly neutralize circulating and tissue-bound TNF-α. These agents are widely used in the treatment of chronic inflammatory diseases, with well-established safety profiles.[12] Small-molecule TNF-α synthesis inhibitors act upstream by suppressing cytokine production and have demonstrated efficacy in experimental models.

Preclinical studies provide strong support for TNF-α inhibition as a therapeutic strategy in aneurysm disease. In murine models of cerebral aneurysm formation, TNF-α knockout animals and those treated with TNF-α inhibitors demonstrate significantly reduced aneurysm incidence and rupture rates.[11,13] Notably, initiation of TNF-α inhibition after aneurysm formation has been shown to prevent aneurysm progression and rupture without affecting initial aneurysm development, suggesting a potential role in stabilizing existing lesions.[11] Similar protective effects

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have been observed in abdominal aortic aneurysm models, where TNF-α inhibition attenuates aneurysm growth, elastic fiber disruption, macrophage infiltration, and MMP expression.[14,15]

Given the central role of TNF-α in aneurysm pathophysiology, the availability of clinically approved anti–TNF-α therapies, and the absence of effective medical treatments for intracranial fusiform aneurysms, a systematic synthesis of existing evidence is warranted. This systematic review aims to evaluate the available clinical and translational evidence examining the relationship between anti–TNF-α therapy and intracranial fusiform aneurysms, with particular focus on aneurysm progression, stability, and rupture risk.

2. Methods

2.1. Eligibility Criteria

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The review protocol was developed a priori, however, the study was not registered in PROSPERO. Studies were eligible for inclusion if they evaluated tumor necrosis factor-α (TNF-α) signaling or anti–TNF-α therapies in relation to intracranial aneurysm disease, with a specific emphasis on fusiform intracranial aneurysms, intracranial dolichoectasia, and vertebrobasilar dolichoectasia.

Eligible study populations included human subjects, animal models, and translational or mechanistic studies (ex vivo or in vitro) provided that the work directly addressed intracranial aneurysm biology. Clinical studies were included if they reported exposure to anti–TNF-α biologic agents—specifically infliximab, adalimumab, etanercept, golimumab, or certolizumab pegol—or other TNF-α–targeting strategies, and evaluated clinical outcomes such as aneurysm growth or progression, rupture, ischemic events, need for intervention, imaging changes, or treatment-related adverse events. Translational and basic science studies were included if they examined TNF-α signaling, inflammatory pathways, macrophage activity, matrix metalloproteinases, or vascular remodeling in the context of intracranial aneurysm formation or progression.

Studies focusing exclusively on saccular intracranial aneurysms without fusiform, dolichoectatic, or non-saccular phenotypes, extracranial aneurysms, or non-aneurysmal cerebrovascular conditions were excluded. Narrative reviews, editorials, commentaries, and protocol-only publications without original data were excluded, though their reference lists were screened for potentially eligible primary studies. Conference abstracts were included only if sufficient methodological and outcome data were available for extraction. Duplicate publications reporting overlapping datasets were consolidated, with the most comprehensive report retained.

2.2. Information Sources

A comprehensive literature search was performed across PubMed/MEDLINE, Embase, and Google Scholar from database inception through the final search date. PubMed searches incorporated structured Medical Subject Headings (MeSH) and free-text terms related to TNF-α biology and anti–TNF therapies combined with intracranial aneurysm terminology. To minimize overrepresentation of saccular aneurysm literature, a secondary fusiform-focused search strategy was implemented emphasizing non-saccular aneurysm phenotypes, including fusiform aneurysms and intracranial dolichoectasia.

Embase searches were conducted using advanced syntax with title and abstract fields prioritized, incorporating therapy-focused, fusiform-specific, translational/mechanistic, and animal-only search layers. Google Scholar searches were performed using simplified keyword combinations pairing TNF-α–related terms and anti–TNF biologics with intracranial aneurysm and fusiform/dolichoectasia terminology. Due to limitations in Boolean handling and semantic expansion within Google Scholar, broad cytokine-only searches yielding non-specific results were de-emphasized in favor of therapy-focused and fusiform-specific combinations. Results from all databases were merged and deduplicated prior to screening.

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2.3. Study Selection Process

All records identified through database searching were imported into Covidence systematic review software for management, deduplication, and screening. Titles and abstracts were screened independently to assess potential eligibility based on predefined inclusion and exclusion criteria. Records deemed potentially relevant proceeded to full-text review. Full-text articles were then assessed for final inclusion, with specific attention to aneurysm phenotype, intracranial location, relevance of TNF-α signaling or anti–TNF therapy, and availability of extractable clinical or mechanistic outcomes.

Disagreements at any stage of screening were resolved through consensus discussion. Studies meeting inclusion criteria were categorized into clinical, translational/mechanistic, or preclinical evidence strata to facilitate structured synthesis of findings across biological and clinical domains.

3. Results

The systematic search across PubMed/MEDLINE, Embase, and Google Scholar identified 368 records. After removal of duplicates and title screening using Covidence systematic review software, 92 unique records remained for abstract review. Following abstract screening, 37 studies underwent full-text evaluation. Fourteen studies met predefined inclusion criteria and were included in the final qualitative synthesis (Figure 1).[16–29]

Of the 14 included studies, 9 evaluated pharmacologic or genetic TNF-α inhibition in experimental models, 3 examined mechanistic TNF-α signaling in human aneurysm tissue, and 2 investigated TNF-α–associated inflammatory pathways in translational settings (Figure 1). Due to heterogeneity in study design, aneurysm phenotype, intervention strategy, and outcome reporting, a meta-analysis was not performed. Findings were synthesized narratively and organized according to clinical, translational, and preclinical evidence domains.

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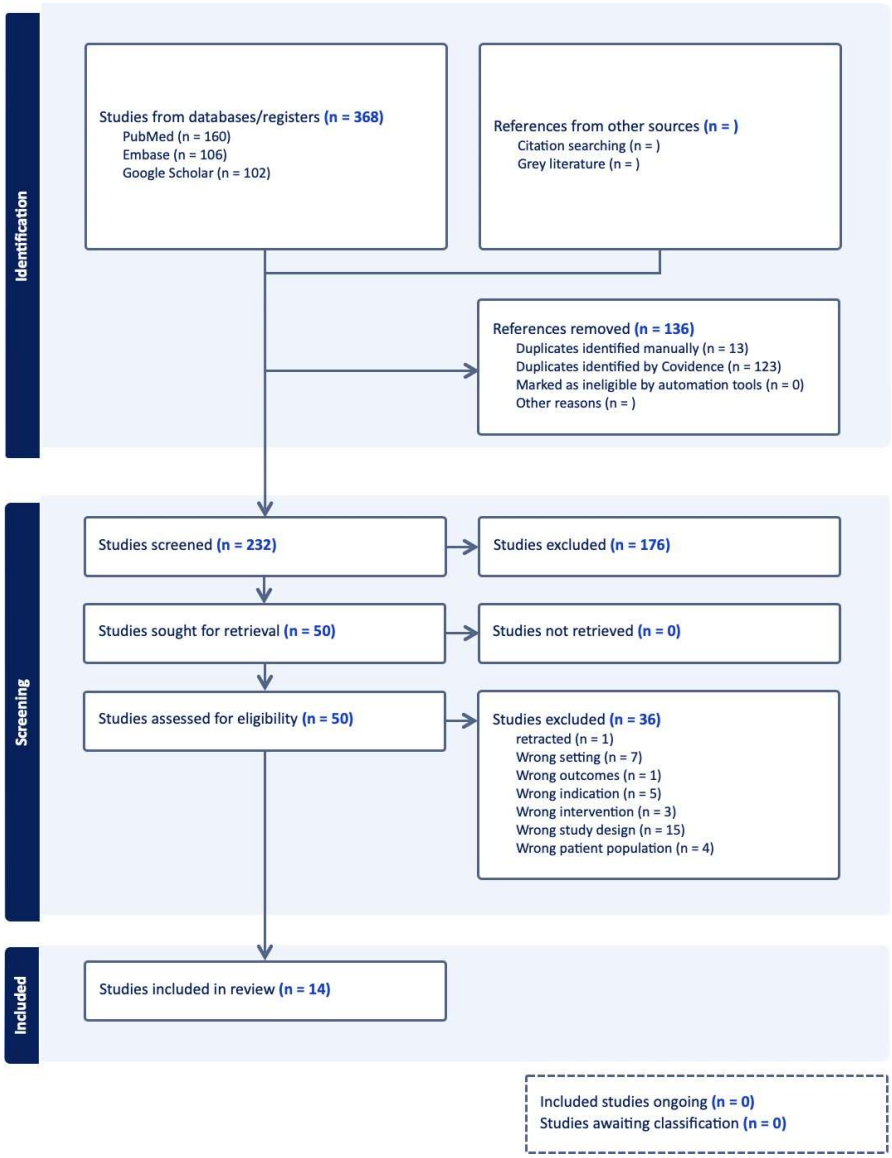

Figure 1. Flowchart showing a systematic search of the literature. A systematic search for scientific literature was performed in February 2026.

3.1. Clinical and Human Tissue Studies

Clinical evidence directly evaluating anti–TNF-α therapy in patients with intracranial fusiform aneurysms was limited. No prospective interventional trials specifically targeting TNF-α signaling in this patient population were identified. However, several human tissue studies consistently demonstrated increased TNF-α expression in aneurysm walls compared with control cerebral arteries.[18,19] Elevated circulating levels of TNF-α and related inflammatory cytokines, including IL-1β, IL-6, and MCP-1, were reported in patients with intracranial aneurysms, with higher levels observed in ruptured lesions compared with unruptured aneurysms.19

Mechanistic associations between TNF-α signaling and inflammatory activation pathways, including NF-κB and TLR-mediated cascades, were also demonstrated in human aneurysm samples.[18,20] These findings support TNF-α as a contributor to aneurysm-associated inflammation but do not yet establish therapeutic efficacy of TNF-α inhibition in fusiform aneurysm populations.

3.2. Translational and Mechanistic Studies

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Experimental investigations demonstrated that TNF-α signaling promotes macrophage recruitment, vascular smooth muscle cell phenotypic modulation, and extracellular matrix degradation.[20–23] In murine models, the TNF-α and Tumor Necrosis Factor Receptor 1 (TNFR1) signaling pathway was shown to be critical for aneurysm formation, with genetic deletion significantly reducing aneurysm incidence.[20]

Prostaglandin E Receptor 2 (EP2) and Nuclear Factor-κB (NF-κB) pathway activation in macrophages was identified as a downstream amplifier of TNF-α–mediated inflammation.[22] Additional mechanistic studies demonstrated that low shear stress induces macrophage infiltration and TNF-α–dependent inflammatory responses in intracranial aneurysm models.[21]

Collectively, these findings identify TNF-α as an upstream regulator of inflammatory cascades driving aneurysmal remodeling.

3.3. Preclinical Animal Studies

Preclinical animal studies provided the strongest evidence supporting a disease-modifying role for TNF-α inhibition. Pharmacologic TNF-α blockade with etanercept suppressed aneurysm formation in murine models.16 Inhibition of TNF-α signaling reduced macrophage infiltration and aneurysm growth in multiple experimental systems.[17,26]

Genetic or pharmacologic suppression of TNF-α–mediated inflammatory pathways reduced aneurysm incidence, attenuated medial thinning, and decreased rupture rates.[20,23,27–29] Notably, TNF-α inhibition initiated after aneurysm formation reduced progression and rupture without preventing initial aneurysm development, suggesting a stabilizing effect on established lesions.[23]

Additional anti-inflammatory compounds targeting TNF-α and NF-κB signaling that including protocatechuic acid, berberine, TWIST1 silencing, and PPAR-γ modulation demonstrated reduced aneurysm growth and inflammatory burden in animal models.[24–29]

Noninvasive neuromodulation strategies suppressing TNF-α signaling similarly reduced rupture rates in murine aneurysm models.[29]

Table 1. Studies Reporting TNF-α Status in Human Intracranial Aneurysms Compared to Control. Cerebral Arteries.

No.	TNF-α Status	Inflammatory Markers and Signaling Pathways	Ref.
1	Higher TNF-α mRNA and protein expression in IA walls compared with control cerebral arteries	Increased IL-1β and IL-6 expression. Increased MCP-1 expression. Activation of TLR4/MyD88 signaling. Enhanced NF-κB nuclear translocation. Upregulation of matrix metalloproteinases and adhesion molecules within aneurysm tissue.	[18]
2	Elevated circulating TNF-α concentrations in patients with intracranial aneurysms. Higher levels observed in ruptured compared with unruptured lesions	Increased systemic IL-1β and IL-6 levels. Elevated MCP-1 expression. Evidence of enhanced NF-κB activation. Systemic proinflammatory cytokine amplification	[19]

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		associated with aneurysm instability.	
3	Upregulated TNF-α–associated inflammatory signaling under low shear stress conditions in aneurysm tissue	Increased macrophage infiltration. Elevated MMP-2 and MMP-9 expression. Enhanced NF-κB activation. Increased transcription of inflammatory mediators contributing to extracellular matrix degradation.	[21]

Table 2. Animal Studies Reporting TNF-α Activation in Intracranial Aneurysm Models Compared to Control Animals.

No.	Animals	TNF-α Activation	Inflammatory Markers and MMPs	IA Features	Ref.
1	Rats	Increased TNF-α mRNA and protein	Increased IL-1β and IL-6 expression. Elevated MCP-1 levels. Increased	Endothelial dysfunction. VSMC apoptosis.	
			expression in IA walls. Enhanced NF-κB activation		
2	Mice	Critical involvement of TNF-α–TNFR1 signaling in aneurysm formation			
3	Mice	Activation of TNF-α–inducible nitric oxide synthase expression. Upregulation of VCAM-1. Increased MMP-2 and MMP-9 expression.	Increased NF-κB activation. Elevated transcription of proinflammatory cytokines. Increased matrix-degrading enzyme expression. TNFR1 deletion suppressed inflammatory cascade.	Increased macrophage recruitment. Elevated Medial thinning. Elastic lamina disruption. Inflammatory cell infiltration.	

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			Reduced aneurysm incidence. Decreased medial degeneration. Reduced inflammatory infiltration in knockout animals.		
			Enhanced aneurysm		
					[17]
					[20]
			dependent EP2–MMP-9 expression. Amplified inflammatory		
			formation.		[22]
		NF-κB pathway in macrophages	cytokine production. Sustained NF-κB activation.	Increased wall degeneration.	
4	Mice	Increased TNF-α expression during aneurysm formation and progression to rupture	Elevated MCP-1 and IL-1β expression. Increased MMP activation. Enhanced NF-κB signaling.	Medial thinning. Elastic fiber fragmentation. Increased rupture rate.	[23]

Table 3. Studies Reporting the Effects of Pharmacological or Genetic TNF-α Modulation on. Intracranial Aneurysm Formation and Rupture in Animals.

No.	Animals	Treatments / Genetic Manipulation	TNF-α Status and Other Pathways	Inflammatory Markers and MMPs	IA Features	Ref.
1	Mice	Etanercept	Reduced TNF-α signaling. Decreased NF-κB activation	Decreased MCP-1 expression. Reduced MMP-2 and MMP-9 levels. Suppressed macrophage-mediated inflammatory cascade.	Reduced aneurysm formation. Reduced rupture rate. Preservation of medial thickness. Preservation of elastic lamina integrity.	[16]
2	Rats	3-Aminobenzamide	Suppressed TNF-α expression. Reduced PARP-	Decreased IL-1β expression. Reduced MMP-2 and MMP-9	Lower aneurysm incidence. Reduced wall	[17]

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			1–mediated inflammatory signaling	levels. Decreased inflammatory cell infiltration.	degeneration.	
3	Mice	TNFR1 knockout	Inhibited TNF-α–mediated NF-κB activation. Suppressed inflammatory amplification	Decreased MMP-9 expression. Reduced cytokine transcription.	Significantly reduced aneurysm formation. Decreased medial thinning.	[20]
4	Mice	EP2–NF-κB pathway inhibition	Suppressed macrophage-specific NF-κB activation downstream of TNF-α	Reduced proinflammatory cytokine expression. Decreased matrix remodeling enzyme levels.	Attenuated aneurysm development. Reduced inflammatory cell accumulation.	[22]
5	Rats	Protocatechuic acid	Inhibited TNF-α/Nrf2/NF-κB signaling pathway	Decreased IL-1β expression. Reduced MMP-2 and MMP-9 levels. Reduced oxidative stress markers.	Reduced aneurysm growth. Reduced medial degeneration. Decreased macrophage infiltration.	[25]
6	Rats	Berberine	Suppressed TNF-α–mediated NF-κB signaling	Reduced MCP-1 expression. Decreased inflammatory cytokine production.	Decreased macrophage infiltration. Reduced aneurysm progression.	[26]
7	Rats	TWIST1 silencing	Reduced NF-κB phosphorylation. Decreased TNF-α levels	Reduced proinflammatory cytokine expression. Decreased apoptotic signaling in VSMCs.	Attenuated aneurysm formation. Preserved VSMC integrity.	[27]
8	Mice	PPAR-γ modulation	Downregulated TNF-α–mediated inflammatory pathways.	Decreased macrophage infiltration. Reduced MMP	Reduced aneurysm formation. Reduced	[28]

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			Reduced NF-κB activity	activation.	rupture rates.	
9	Mice	Vagus nerve stimulation	Suppressed systemic and local TNF-α signaling	Reduced inflammatory cytokine expression. Decreased NF-κB activation.	Decreased rupture rates in established aneurysms. No effect on initial aneurysm formation.	[29]

4. Discussion

This systematic review synthesizes clinical, translational, and preclinical evidence supporting TNF-α–mediated inflammation as an important mediator to intracranial aneurysm pathobiology, including fusiform and dolichoectatic phenotypes. Human aneurysm tissue studies demonstrate higher TNF-α mRNA and protein expression in intracranial TNF-α concentrations in serum are also elevated in patients with intracranial aneurysms, and tend to have higher levels in ruptured compared with unruptured lesions (Table 1).[19] These elevations are accompanied by increased Interleukin -1β and Interleukin-

6 expression, enhanced MCP-1 levels, activation of Toll-like Receptor 4 and Myeloid Differentiation Primary Response 88 signaling, and NF-κB activation within aneurysm tissue (Table 1).[18,19,21]

Across experimental models, TNF-α activation was associated with increased macrophage infiltration, upregulation of Matrix Metalloproteinase-2 and Matrix Metalloproteinase-9, elevated inducible nitric oxide synthase , and amplified NF-κB signaling (Table 2).[20,23] In murine models, Tumor necrosis factor receptor 1 (TNFR1) signaling was shown to be critical for aneurysm formation, and TNFR1 deletion suppressed inflammatory cascade activation and reduced aneurysm incidence (Tables 2 and 3).[20] These inflammatory processes corresponded with medial thinning, elastic lamina fragmentation, endothelial dysfunction, and increased rupture rates in untreated animals (Table 2).[23]

Preclinical inhibition studies provide strong functional evidence of causality. Pharmacologic TNF-α blockade with etanercept reduced NF-κB activation, decreased MCP-1 expression, lowered MMP-2 and MMP-9 levels, and preserved medial thickness and elastic lamina integrity (Table 3).16 This intervention was associated with reduced aneurysm formation and decreased rupture rates in murine models.[16] Similarly, TNFR1 genetic knockout significantly reduced aneurysm formation and suppressed inflammatory cytokine transcription (Table 3).[20] Inhibition of macrophage-specific EP2–NF-κB signaling downstream of TNF-α attenuated aneurysm development and reduced inflammatory cell accumulation (Table 3).[22]

Additional pharmacologic agents targeting TNF-α–mediated pathways produced concordant results. Protocatechuic acid reduced IL-1β expression, decreased MMP-2 and MMP-9 levels, and limited aneurysm growth and medial degeneration in rat models (Table 3).[25] Berberine suppressed TNF-α–mediated NF-κB signaling, reduced MCP-1 expression, and decreased macrophage infiltration and aneurysm progression (Table 3).[26] TWIST1 silencing reduced NF-κB phosphorylation, decreased TNF-α levels, and attenuated aneurysm formation while preserving vascular smooth muscle cell integrity (Table 3).27 Collectively, these interventions consistently reduced aneurysm incidence, limited wall degeneration, and lowered rupture rates compared with untreated controls.[16,20,23,25,26]

Importantly, several studies demonstrated that TNF-α suppression after aneurysm induction reduced progression and rupture, rather than solely preventing initiation (Table 3).[16,23] This

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distinction is clinically relevant for intracranial fusiform aneurysms, which are often diagnosed after structural dilation has occurred and currently lack disease-modifying medical therapies.

Despite strong mechanistic and preclinical evidence, clinical data remain limited.

No randomized clinical trials evaluating anti–TNF-α biologic therapy in patients with intracranial fusiform aneurysms were identified. Observational human studies confirm elevated TNF-α activity, NF-κB activation, and increased proinflammatory cytokine expression within aneurysm tissue (Table 1).[18,19,21] However, these findings establish association rather than therapeutic efficacy. Additionally, heterogeneity in aneurysm morphology across studies that included saccular, fusiform, and dolichoectatic phenotypes limited direct extrapolation specifically to fusiform lesions.

TNF-α plays an important role in immune regulation and host defense.[12] Long-term systemic inhibition is associated with increased risk of infection and malignancy.[12] Therefore, translation of anti–TNF-α therapy into cerebrovascular disease requires careful evaluation of safety, dosing, timing, and patient selection. Experimental evidence suggests TNF-α signaling contributes particularly to inflammatory amplification, extracellular matrix degradation, and rupture progression (Tables 2 and 3),[20,23] which could indicate that therapeutic targeting may be most effective in progressive or late-stage aneurysms rather than in early lesion initiation.

Future investigations should include prospective observational studies correlating circulating TNF-α levels with aneurysm growth and rupture risk (Table 1).[19] Early-phase clinical trials evaluating safety, biomarker modulation, and imaging-based endpoints in high-risk fusiform aneurysm populations are warranted. Biomarker-guided strategies leveraging TNF-α and NF-κB activation status may help identify patients most likely to benefit from targeted modulation.[19]

Importantly, anti–TNF-α agents are already FDA-approved with established pharmacokinetics and safety profiles in chronic inflammatory diseases.[12] This creates a realistic opportunity for therapeutic repurposing in high-risk intracranial fusiform aneurysm populations, potentially accelerating translational implementation compared with development of novel biologics.

5. Conclusions

Translational human tissue studies demonstrate elevated TNF-α expression, increased IL-1β and IL-6 levels, MCP-1 upregulation, and NF-κB pathway activation within intracranial aneurysm walls (Table 1).[18–21] Experimental models confirm that TNF-α activation promotes macrophage infiltration, MMP-2 and MMP-9 upregulation, medial thinning, elastic lamina disruption, and increased rupture incidence (Table 2).[20,23]

Pharmacologic and genetic TNF-α inhibition—including etanercept administration, TNFR1 deletion, EP2–NF-κB pathway suppression, and small-molecule anti-inflammatory compounds—consistently reduces aneurysm formation, limits growth, preserves vascular wall structure, and lowers rupture rates in preclinical models (Table 3). [16,20,23,25,26]

However, clinical data in patients with intracranial fusiform aneurysms remain insufficient to support routine therapeutic use. Carefully designed prospective studies and early-phase clinical trials are necessary to define the safety, timing, and efficacy of TNF-α–targeted therapies in this high-risk population.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org.

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