The Journal of Rheumatology 2025;52 Suppl 3:83–6
doi:10.3899/jrheum.2025-0528
First Release August 15 2025

The Journal of Rheumatology

A New Mouse Model of Psoriatic Arthritis

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ABSTRACT. Polymorphisms in the *TNFAIP3* locus encoding the A20 protein are strongly associated with psoriatic skin and joint disease. Reduced A20 expression, driven by both genetic and epigenetic factors, underscores its critical role as a negative regulator of psoriatic disease (PsD). Our recent study using a germline knockin mouse model harboring a mutation in A20's seventh zinc finger, which impairs A20 binding to linear (M1) ubiquitin, revealed a spontaneous phenotype resembling psoriatic arthritis. These mice demonstrated sustained nuclear factor–κB signaling in response to transient tumor necrosis factor stimulation, leading to inappropriate transcription of mid- and late-response inflammatory genes. These findings highlight the role of dysregulated innate immune-signaling kinetics as a potential driver of PsD pathogenesis. These findings, together with distinct inflammatory mouse models resulting from temporally extended inflammatory gene activation, highlight the role of dysregulated innate immune-signaling kinetics as a potential driver of tissue inflammation with relevance to psoriatic skin and joint disease. This newly developed mouse model of PsD was presented at the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) 2024 annual meeting.

Key Indexing Terms: GRAPPA, innate immunity, NF-κB, psoriasis, psoriatic arthritis

Genome-wide association studies have identified polymorphisms in a number of loci associated with an increased risk of psoriatic skin and joint disease.[1-5] Understanding how these polymorphisms contribute to cutaneous psoriasis (PsO) and psoriatic arthritis (PsA) not only sheds light on the molecular pathogenesis of these diseases but can also inform precision medicine approaches aimed at matching treatment modalities to an individual patient's genotype. Among risk loci for psoriatic disease (PsD), polymorphisms in the *TNFAIP3* locus, which encodes the protein A20, have been strongly associated with both cutaneous PsO and PsA.[1-4] These polymorphisms reduce expression or function of A20.[6,7] Further, independent of their underlying genetics, patients with PsO display reduced levels of A20 in their skin compared to healthy individuals, suggesting epigenetic mechanisms may affect tissue A20 expression in PsD.[8-10]

The key role of A20 in maintaining immune homeostasis in humans has also been revealed by the description of individuals carrying heterozygous coding mutations of the A20 gene, often leading to reduced protein expression and early truncations.[11] These patients with A20 haploinsufficiency (termed HA20) present with an early-onset multisystem inflammatory disorder that most commonly affects mucous membranes, skin, intestines, and joints. Joint involvement, which affects nearly a third of patients with HA20, typically manifests as juvenile-onset polyarthritis.[11-14] Interestingly, even within a single familial cohort, the presentation of disease can be diverse, suggesting complex interaction of A20 dysfunction with genetic or environmental background.[13]

Genetic animal models of A20 dysregulation show spontaneous inflammatory phenotypes, underscoring their value as powerful tools to elucidate the physiologic functions of A20. Germline deficiency of A20 leads to perinatal death of mice from massive multiorgan inflammation.[15] Tissue-specific deletion of A20, achieved by crossing LoxP-bearing A20 alleles with cell type–specific Cre transgenes, leads to distinct spontaneous inflammatory phenotypes. These findings highlight that disruption of A20-mediated immune homeostasis within defined cellular compartments can elicit distinct inflammatory outcomes, as previously reviewed.[16] Tissue-specific knockout of A20 in myeloid cells develops early enthesitis followed by an erosive polyarthritis that resembles rheumatoid arthritis, although no spontaneous skin or nail inflammation was observed in this model.[17,18] Additionally, 2 independent studies investigating tissue-specific deletion of A20 in dendritic cells reported divergent spontaneous inflammatory outcomes that included arthritis, although no accompanying skin inflammation was reported.[19,20] One model developed spontaneous colitis and a seronegative arthritis, resembling inflammatory bowel disease–

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Accepted for publication May 7, 2025.

associated arthritis, whereas the other developed features of systemic lupus erythematosus, including dsDNA autoantibodies accompanied by glomerulonephritis and autoimmune arthritis. These findings suggest that the consequences of cell type–specific A20 deficiency may be modulated by complex interactions with the microbiota. Collectively, human and animal studies strongly suggest that A20 is a key negative regulator of spontaneous inflammation as well as of human psoriatic skin and joint disease. However, the molecular mechanisms that connect A20 dysregulation to cutaneous PsO and PsA are poorly understood.

In our recent work, we used mouse models to identify the biochemical mechanism by which A20 restricts PsD.[21] A20 possesses multiple domains with distinct enzymatic and nonenzymatic actions on ubiquitin posttranslational modifications (Figure 1). By virtue of its effect on ubiquitin-mediating signaling, A20 plays a critical role in regulating signal transduction downstream of multiple innate immune receptors, including interleukin (IL)-1–like receptors, IL-17 receptor, tumor necrosis factor (TNF) receptors, Toll-like receptors, NOD-like receptors, and C-type lectin receptors.[16]

Germline knockin transgenic mice, in which specific residues are mutated to destroy the function of particular domains while leaving the remaining domains intact, give us means to investigate the physiological function of A20. Prior germline knockin mouse mutants targeting distinct domains that enzymatically cleave or synthesize ubiquitin chains failed to demonstrate spontaneous inflammatory pathology, suggesting that these domains were not critical for restricting spontaneous PsD in vivo[22-24] (Figure 1). In recent years, the C-terminal structural domain of A20, the seventh in a series of adjacent zinc fingers (ZF7), has been shown to noncatalytically bind to ubiquitin with a strong affinity for ubiquitin chains that are attached end-to-end via the first methionine (M1) residue in a "linear" arrangement.[25,26] In our recent work, we investigated the physiological role of A20's ZF7 by generating a $A20^{ZF7}$ germline knockin mouse model in which this domain is no longer able to bind linear ubiquitin.[21]

These $A20^{ZF7}$ mice developed spontaneous dactylitis and nail loss, clinically manifesting at 5 weeks of age and progressively encompassing all digits by 3 months of age (Figure 2). These findings occurred with 100% penetrance in both male and female mice. Histological examination of tissues showed key features of PsA, including enthesitis, distal osteolysis, and areas of bone formation.[21] In addition to sharing phenotypic features with human PsA, disease in $A20^{ZF7}$ mice reflected the molecular pathogenesis of human PsD, as TNF and IL-17A involvement were required for disease.[21]

To understand how mutation of A20's ZF7 triggers spontaneous inflammation, we studied the kinetics of nuclear factor (NF)-κB signaling downstream of TNF, a key psoriatic cytokine. Prior studies have shown that transactivation of inflammatory genes in response to innate immune stimuli, such as TNF, in both stromal and immune cells occurs in a temporally phased manner.[27,28] Certain genes are transactivated within minutes (early phase), whereas the expression of others requires 2 to 6 hours to increase (mid and late phase; Figure 3A). This phasing emerges from cell intrinsic temporal differences in how inflammatory mRNA transcripts are processed, as well as secondary signaling effects from cytokines synthesized in temporally earlier phases.[27-29] Remarkably, in response to transient TNF stimulation, cells from wild-type mice do not transactivate mid- and late-phase gene programs.[21] However, we found that cells from $A20^{ZF7}$ knockin mice robustly transactivate these gene programs in response to transient TNF stimulation (Figure 3B).[21] Mechanistically, this inappropriately extended inflammatory signaling resulted from defective recruitment of $A20^{ZF7}$ mutant

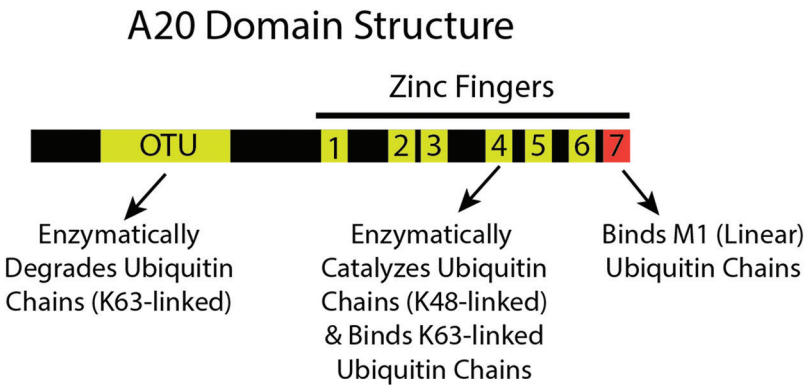

Figure 1. Domain structure of A20. A20 possesses an N-terminal OTU domain followed by 7 consecutive ZFs. The C-terminal ZF7, highlighted in red, nonenzymatically binds to linear ubiquitin. The knockin mouse model described here mutates residues within this domain to prevent binding to ubiquitin. Other well-characterized biochemical domains include the N-terminal OTU domain, which acts as a deubiquitinase, enzymatically degrading ubiquitin chains with a preference for ubiquitin chains polymerized via lysine 63 (K63-linkage). ZF4 acts as a ubiquitin ligase, generating ubiquitin chains linked via lysine 48 (K48-linkage) and binds to ubiquitin chains linked via lysine 63 (K63-linkage). Prior knockin mouse models disrupting the OTU or ZF4 domains did not lead to spontaneous inflammatory tissue pathology.[13-15] OTU: ovarian tumor; ZF: zinc finger.

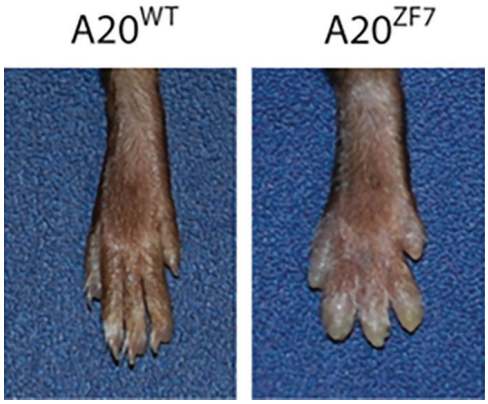

Figure 2. Clinical phenotype of A20^{ZF7} mice. Clinical photos of A20^{WT} and A20^{ZF7} mice at 12 weeks of age. A20^{ZF7} mice show dystrophy and loss of nail plate as well as dactylitis. WT: wild-type; ZF7: seventh zinc finger.

protein to the catalytically active and linearly ubiquitinated IκB kinase complex, the central kinase that triggers NF-κB signaling.

Our findings align with prior mouse models of inflammatory arthritis that temporally lengthen inflammatory signaling by extending the expression of inflammatory transcripts. These studies highlight a potential role for dysregulation of innate immune-signaling temporal kinetics and the accompanying inappropriate lengthening of signaling in the pathogenesis of PsD. Many inflammatory transcripts possess AU-rich elements (ARE) in their 3′ untranslated regions that shorten mRNA's half-life, ensuring that these transcripts do not temporally persist following their transactivation.[30] It is notable that in mouse models that disrupt ARE-mediated destabilization of inflammatory transcripts, the mice develop spontaneous inflammatory disease. For example, the TNF$^{\Delta ARE}$ mouse, which possesses mutations that disrupt the ARE of the *TNF* transcript by lengthening its half-life, develops spontaneous inflammatory arthritis.[31,32] Recent reports showed that mice deficient in ZFP36, a protein that binds to the AREs of multiple inflammatory transcripts to promote their destabilization, develop spontaneous inflammatory skin and joint disease resembling PsO and PsA.[33]

Microtrauma has been hypothesized to be a driver of psoriatic skin and joint disease.[34] In healthy individuals, stromal and immune cells may be able to ignore these transient inflammatory stimuli, whereas tissues in individuals with PsD may initiate inappropriately extended signaling responses. Most current therapeutics aim to eliminate signaling downstream of specific cytokines or their signaling mediators. Shortening temporal length of signaling by targeting molecules that broadly affect signaling temporal persistence may offer a complementary strategy for treating PsD.

It is notable that inflammatory pathology is primarily observed on the distal digit tip of A20^{ZF7} mice, an anatomical location where the nail matrix is in proximity to the distal synovio-entheseal complex.[21,34] This location likely encounters frequent transient microtrauma throughout the murine lifespan. This anatomically complex region of mammals includes multiple lineages of stromal cells within the skin, synovium, and tendons, together with resident and circulating immune cells.[35] We are actively investigating which of these tissues or cell types drive pathology in mouse models of A20 dysfunction.

ACKNOWLEDGMENT

We thank DerMEDit (www.dermedit.com) for editing services in preparation of this manuscript.

FUNDING

This work was supported by a National Institutes of Health grant (no. K08AR077065), the Arthritis National Research Foundation, and the Dermatology Foundation.

COMPETING INTERESTS

VC has received research grants from AbbVie, Amgen, and Eli Lilly; has received honoraria for advisory board member roles from AbbVie, BMS, Eli Lilly, Fresenius Kabi, Janssen, Novartis, and UCB; and his spouse is an employee of AstraZeneca. WL has received research grant funding from Amgen, Janssen, Leo, and Regeneron. The remaining authors declare no conflicts of interest relevant to this article.

ETHICS AND PATIENT CONSENT

Institutional review board approval and patient consent were not required.

PEER REVIEW

As part of the supplement series GRAPPA 2024, this report was reviewed internally and approved by the Guest Editors for integrity, accuracy, and consistency with scientific and ethical standards.

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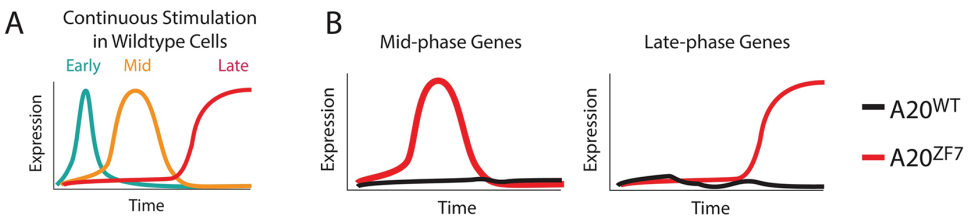

Figure 3. Schematic of phased inflammatory gene expression and its dysregulation in A20^{ZF7} cells. (A) In wild-type cells, specific genes are activated in a temporally phased manner in response to continuous stimulation with cytokines such as TNF or IL-1. These genes can be grouped into early-, mid-, and late-phased genes. (B) When cells are transiently exposed to cytokines such as TNF for ~15 minutes, mid- and late-phase gene programs are never activated in wild-type cells; however, such transient exposure robustly activates these genes in A20^{ZF7} cells. IL-1: interleukin 1; TNF: tumor necrosis factor; ZF7: seventh zinc finger.

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