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Mini review

Emerging roles for TNIP1 in regulating post-receptor signaling

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ABSTRACT

A vast number of cellular processes and signaling pathways are regulated by various receptors, ranging from transmembrane to nuclear receptors. These receptor-mediated processes are modulated by a diverse set of regulatory proteins. TNFα-induced protein 3-interacting protein 1 is such a protein that inhibits both transduction by transmembrane receptors, such as TNFα-receptor, EGF-R, and TLR, and nuclear receptors' PPAR and RAR activity. These receptors play key roles in regulating inflammation and inflammatory diseases. A growing number of references have implicated TNIP1 through GWAS and expression studies in chronic inflammatory diseases such as psoriasis and rheumatoid arthritis, although TNIP1s exact role has yet been determined. In this review, we aim to integrate the current knowledge of TNIP1s functions with the diseases in which it has been associated to potentially elucidate the role this regulator has in promoting or alleviating these inflammatory diseases.

1. Introduction

Receptor-mediated signals and the changes in gene expression they instigate are regulated by the availability of receptor ligands as well as supernumerary checks on post-receptor pathways thus providing a more rheostat-type control rather than an all-on or all-off switch. The TNFα-induced protein 3 (TNFAIP3)-interacting protein 1 (TNIP1, also known as ABIN-1, Naf1 and VAN) appears to be one of these pathway-modulating factors. Known as a human cellular protein capable of interaction with the HIV proteins nef and matrix [1,2], it was also discovered to interact with the cytoplasmic protein A20 (also known as TNFAIP3) and to dampen subsequent NF-κB signaling following TNFα receptor (TNFα-R) activation [3]. Even with this latter function well established, TNIP1s interaction portfolio continues to expand [3–7]. For instance, we have found it acts as a corepressor of ligand-bound retinoic acid receptors (RARs) [8] and peroxisome proliferator activated receptors (PPARs) [9], while other researchers discovered it prevents EGF-R-induced ERK2 nuclear translocation [10]. Additionally, genetic ablation of TNIP1 in mice [11] has suggested the phenotype due to its loss may not simply be the inverse of over-expression studies. Unexpectedly, TNIP1 null cells had levels of NF-κB-dependent gene expression similar to wild-type cells. Nevertheless, in these cells, another post-TNFα receptor pathway was affected, leading to increased apoptosis [11]. These roles for TNIP1 in model systems raise the questions of what do we know of TNIP1 in human disease, and, how might one correlate TNIP1 reduction of TNFα signaling with other findings of altered TNIP1 expression levels in inflamed tissues. The aim of this review is to provide some perspective by examining the association of TNIP1 and disease states in human genetic studies along with candidate signaling pathways based on cellular and molecular studies.

2. TNIP1 and associated diseases and phenotypes

2.1. Implications from GWAS and array studies

Current connections between TNIP1 and human pathologies cross several tissues including skin, connective tissue, possibly blood vessels and some internal organs. These associations derive from high throughput approaches such as genome-wide association studies (GWAS) and expression microarrays [12–18] (Table 1). Whether through sequence variations or expression levels, these approaches have linked TNIP1 with psoriasis, systemic lupus erythematosus (SLE), systemic sclerosis (SSc), rheumatoid arthritis (RA) and leukemia/lymphoma. Although family genealogies and twin studies have documented hereditary components or shared genetic loci for these pathologies [19–24], no one gene such as TNIP1 has been identified as definitively causative for any one of them, unlike the variant coding sequence for a "classic" single-gene disease, viz. hemophilia and mutations in genes for clotting factors VIII or IX. Further compounding the study of psoriasis, SLE,

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Table 1
TNIP1 and associated diseases.

Disease	TNIP1 association	Experimental approach	Reference
Psoriasis	Intronic SNP; increased expression	GWAS; gene expression microarray	Nair et al. [13]; Psoriasis Consortium [33]; Ellinghaus et al. [30]
Psoriatic arthritis	Intronic SNP	GWAS	Bowes et al. [29]
Systemic lupus erythematosus	Intronic SNP	GWAS	Kawasaki et al. [17]
Systemic sclerosis	Intronic SNP	GWAS	Allanore et al. [18]
Leukemia–lymphoma	Splice variants	RT-PCR and sequencing	Shiote et al. [32]
Leukemia–lymphoma	Point or frameshift mutations	PCR and sequencing	Dong et al. [41]
Rheumatoid arthritis	Increased expression	Gene expression microarray	Gallagher et al. [12]

and RA is the participation of often multiple cell types, broadly grouped as non-immune and immune, suggesting TNIP1 expression changes specific to any one of them might confer some disease pathology to the affected organ. Although no human disease correlate has yet been identified with the pathology seen in the TNIP1 mouse knockout [11] (see Section 2.3), a lupus-like autoimmune disease was seen in a TNIP1 mutant mouse knock-in [25], which is consistent with current genome wide association scans (GWAS). Additionally, the inflammation-associated defects seen using both in vitro and in vivo experimental systems are consistent with current reports of TNIP1 alterations associated with human auto-immune and chronic inflammatory diseases. TNIP1s wide tissue distribution [2,9,26] and involvement in a number of receptor-mediated signaling pathways would likely extend impact of its altered function to non-immune cells. For instance, we found TNIP1 antibody staining in both stratified epithelial cells and germinal centers of human tonsil [26]. More clearly defined roles for TNIP1 in normo- and patho-physiology and will benefit from organ- and cell-specific knockout systems.

The *TNIP1* gene has been implicated in psoriasis, SLE and SSc through at least three independent GWAS reports. In each case however, the strongest disease-associated single nucleotide polymorphisms (SNP) were in non-coding regions. In the psoriasis study [13], despite strong association with the disease (*P*-value 1×10^{-20}) and ~1.5 fold increase in TNIP1 expression between lesioned and uninvolved skin (i.e., tissues from the same individual), the SNP was several kilobases upstream from the *TNIP1* locus. Psoriasis is classically recognized as epidermal keratinocyte hyperproliferation with incomplete differentiation, incomplete barrier formation, and immune cell infiltration [27]. Notably, there is often the comorbidity of psoriatic arthritis, a chronic inflammatory disease where immune cells target the patient's joints promoting cartilage breakdown and bone damage [28]. It is not unexpected then that SNP alleles were also confirmed for psoriatic arthritis [29,30].

Similar to psoriasis, SNPs in non-coding regions were also disease associated with SSc. Three different TNIP1 SNPs were identified in European populations in the second GWAS report for SSc [18]. Intriguingly, when TNIP1 mRNA and protein levels were assessed from cultured dermal fibroblasts of SSc patients, a ~1.7-fold decrease was observed. A separate GWAS study also identified SNPs in SLE. Two TNIP1 intronic SNP variants were found in SLE patients from Chinese Han, Caucasian, and Japanese populations, with the latter two groups having the same SNP [14,15,17]. Unlike the altered expression of TNIP1 in psoriasis and SSc, there was no TNIP1 mRNA change associated with this SLE SNP [17]. However, Kawasaki and colleagues suggested the SNP location in intron 1 could impact TNIP1 splicing possibly affecting the use of alternative exons 1A and B with exon 2 and thereby contributing to the numerous splice variants of TNIP1 [31,32] with as yet unrecognized consequences. Perhaps reflecting the polygenic nature of these pathologies, it is interesting to note that a protein–protein interaction partner for TNIP1, TNFAIP3 (also known as A20), is also a susceptibility locus for psoriasis [13,33], SLE [14,34], and RA [35,36]. Most challenging in understanding these results will be to appreciate how SNP variants in non-coding regions can go from association with the disease to at least contributory if not causative. Some context for that comes from a recent report that about 88% of trait or disease-associated SNPs are located in gene introns or intergenic regions [37]. Far from being innocuous spacers between coding regions of genes, introns are now recognized as possible sites of transcription-regulating factors at the DNA level and/or potential effectors of splicing at the RNA level [38,39]. Likewise, proximal or intergenic regions, especially those covering the disease-associated gene's promoter/enhancer region, may affect expression levels or tissue-specific expression [37]. Most recently, copy number variations were reported for TNFAIP3 and TNIP1 suggesting other forms of genome-wide analyses could prove productive in relating these genes to the disease states [40].

In addition to gene analysis, TNIP1 mRNA expression has been analyzed from several human cell lines and tissues. Several splice variants having either 5′ truncated ends or lacking specific exons were detected in samples derived from patients with acute myeloid leukemia (AML) [32]. Although variant 5′ ends have been mapped to the use of alternative first exons, the 3′ truncations described in these samples are the first of their kind to be reported. Most of the splice variants did not confer changes in amino acid sequence. However, one variant lacking exons 16 and 17 was less effective at reducing NF-κB activity. Decreased TNIP1 mRNA levels, for with full-length or splice variants, were observed in AML patient samples post chemotherapy treatments. Separately, several TNIP1 mutations have been detected in gastrointestinal diffuse large B cell lymphomas [41]. These sequence alterations are either point or frame-shift mutations, the latter resulting in a protein truncation. One mutant in particular, causing a glutamic acid to lysine change (E476K), lost its NF-κB inhibitory properties; other missense mutations did not alter this TNIP1 property. Thus, sequence variations, either at the mRNA level possibly affecting message stability, exon content, or amino acid sequence could impact ultimate TNIP1 protein function. Additionally, we should consider that there could be functional consequence to even wild-type TNIP1 protein if its levels or post-translation processing, e.g., phosphorylation (see Sections 2.3 and 5.2) were altered.

In contrast to other TNIP1 associated diseases, the connection between *TNIP1* and RA appears strictly at the expression level, not at a susceptibility locus or nucleotide mutation. Three SNP type GWAS reports [17,36,42] concluded loci-disease association(s) did not meet the cut-offs used for the analyses. However, when compared to knee synovial membrane biopsies from osteoarthritis patients, similar samples from patients with RA showed a 2.5–3.5 fold TNIP1 mRNA increase. Osteoarthritis and RA are referred to as non-inflammatory vs. inflammatory forms of the disease, respectively. Consistent with this inflammatory association, TNIP1 was one of the genes with increased expression following TNFα treatment of cultured synovial fibroblasts [12]. Nevertheless, TNFα-increased TNIP1 expression may be tissue specific by following one of multiple post-TNFα-receptor signaling pathways.