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# Expression of transcription factor zinc-binding protein-89 (ZBP-89) is inhibited by inflammatory cytokines

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**Abstract:** Zinc-binding protein-89 (ZBP-89; ZNF148, BERF-1, BFCOL-1) is a zinc-finger transcription factor of the Kruppel family. It has been shown to regulate the expression of a number of genes, acting as either an activator or repressor of gene expression, depending on the context. It is over-expressed in several cancers, but has been shown to be involved in apoptosis and to have a negative influence on cell growth in part by interactions with p53. Previously, ZBP-89 was shown to activate transcription of the matrix metalloproteinase-3 (MMP-3) gene by binding to a polymorphic promoter element in competition with nuclear factor  $\kappa$ B (NF- $\kappa$ B). NF- $\kappa$ B is known to be a key regulator of the inflammatory response, but relatively little is known about regulation of ZBP-89. In order to ascertain whether ZBP-89 is regulated during inflammation, we designed experiments to determine whether and to what extent ZBP-89 levels are affected by inflammatory cytokines. Here we show that ZBP-89 mRNA and protein expression are significantly inhibited in human fibroblasts by the inflammatory cytokine interleukin-1 $\beta$ . Since any change in the levels of ZBP-89 would presumably impact the regulation of MMP-3 and other ZBP-89 target genes, these results provide important insight into mechanisms involved in fine-tuning the immune response.

**Keywords:** ZBP-89, ZNF148, BERF-1, IL-1, TNF, fibroblasts

## Introduction

Zinc-binding protein-89 (ZBP-89; ZNF148, BERF-1, BFCOL-1) is a ubiquitously expressed zinc-finger transcription factor of the Krüppel family. It has been shown to regulate the expression of a number of genes, acting as either an activator<sup>1-4</sup> or repressor<sup>5-10</sup> of transcription, depending on the context. When ZBP-89 is a repressor of gene expression, it often accomplishes this by competing for an overlapping binding site with another transcription factor, usually Sp1,<sup>5,7,11</sup> although the protein does also have a repression domain.<sup>8</sup>

The case of human matrix metalloproteinase 3 (MMP-3) is somewhat different, however, in that ZBP-89 has been shown to activate transcription in competition with NF- $\kappa$ B for binding to a polymorphic 5T/6T site in the promoter.<sup>4,12</sup> This site was originally identified as a repressor element, with the 6T version being a more effective repressor than the 5T in transiently transfected fibroblasts.<sup>13</sup> In COS-1 cells, over-expressed ZBP-89 activated the 5T promoter more efficiently than the 6T, while NF- $\kappa$ B repressed both.<sup>12</sup> This polymorphism is functionally significant in that it has been shown both to influence levels of MMP-3 in tissues<sup>14,15</sup> and to be associated with increased risk or severity of several disease states.<sup>16-19</sup> For example, individuals homozygous for the 6T site have been shown to express less MMP-3 protein in aortic

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wall and dermal tissues and to have more rapid progression of atherosclerosis,<sup>14,15,18,19</sup> while individuals homozygous for the 5T site express more protein in tissues and are at increased risk for myocardial infarctions and aneurysms.<sup>16,17,20</sup>

Since the role of the polymorphism in determining the levels of MMP-3 protein expression likely depends on the relative concentrations of NF- $\kappa$ B and ZBP-89 under various conditions, it is important to understand how each is regulated. While NF- $\kappa$ B is the prototypical pro-inflammatory response factor, responsible for coordinating the induction of a variety of genes in response to pro-inflammatory cytokines, relatively little is known about regulation of ZBP-89. Here we show that ZBP-89 mRNA and protein levels are decreased by inflammatory cytokines IL-1 $\beta$  and TNF- $\alpha$  in human gingival fibroblasts isolated from patients with periodontitis, and by IL-1 $\beta$  and lipopolysaccharide (LPS) in WI-38 normal human diploid fibroblasts. Interestingly, TNF fails to inhibit ZBP-89 expression in WI-38 cells, suggesting some cell type specificity in the regulation of ZBP-89.

## Materials and methods

### Cell culture

Human gingival tissue from patients undergoing periodontal surgery was obtained from Newtown Dental Associates in Newtown, PA. The tissue was processed by enzymatic dispersion to produce primary fibroblast cultures (HGF). Cells were maintained in Eagle's minimal essential medium (EMEM) supplemented with 10% fetal bovine serum and antibiotic/antimycotic (penicillin, streptomycin, amphotericin; Gibco BRL/Invitrogen, Carlsbad, CA, USA). Cells between passages 3 and 5 were used for experiments. WI-38 cells were obtained from ATCC (Manassas, VA, USA) and maintained as suggested.

### RNA isolation and real-time polymerase chain reaction

Cells were serum-deprived for 16 hours in serum-free EMEM supplemented with 10% ITS (insulin, transferrin, sodium selenite; Sigma-Aldrich, St. Louis, MO, USA) prior to the addition of the indicated doses of cytokines. IL-1 $\beta$  was obtained from DuPont-Merck Corp (Wilmington, DE, USA), IL-4 from Promega (Madison, WI, USA), and TNF $\alpha$  from Sigma-Aldrich. LPS was obtained from Calbiochem (San Diego, CA) and epidermal growth factor (EGF) from Biosource International, (Camarillo, CA, USA). Total RNA was isolated at the indicated times using the RNAqueous-4PCR kit (Ambion/Applied Biosystems,

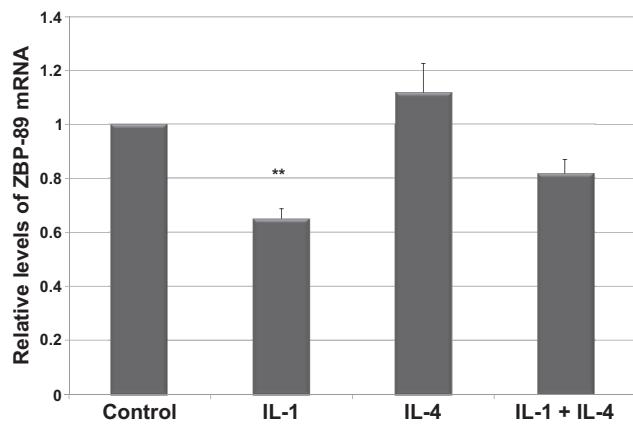
Austin, TX, USA) according to manufacturer's instructions and reverse transcribed into cDNA using the High Capacity cDNA Archive Kit (Applied Biosystems) and Thermal Cycler Genius. Real-time polymerase chain reactions (PCR) consisted of 2  $\mu$ l of cDNA, 6.8  $\mu$ l of H<sub>2</sub>O, 10  $\mu$ l of the Premix *Ex Taq*<sup>TM</sup> (master mix and 0.4  $\mu$ l ROX Reference Dye; TAKARA, Madison, WI, USA) and 0.8  $\mu$ l probes (ZNF148, glyceraldehyde-3-phosphate dehydrogenase [GAPDH]; Applied Biosystems). Real-time PCR analysis was done using the Applied Biosystem 7500 Real Time PCR system. Reactions were done in triplicate and results were normalized to GAPDH.

### Protein isolation and Western blotting

Whole cell extracts were prepared using the Nuclear Extraction Kit from Active Motif (Carlsbad, CA, USA) using the suggested procedure for whole cell extraction, and quantified in mini-Bradford assays (Pierce Biotech, Rockford, IL, USA). Thirty  $\mu$ g extract were separated on 10% SDS-polyacrylamide gels. Proteins were transferred to Immobilon-P Transfer Membrane (Millipore, Billerica, MA, USA) and the membrane was blocked overnight with Super Block blocking buffer (Pierce Biotech). The blot was then incubated with anti-ZBP-89 (Santa Cruz, Santa Cruz, CA, USA) antibody diluted 1:1000 in Super Block for one hour at room temperature. After washing three times in TBST (20 mM Tris-HCl pH 7.5, 150 mM NaCl, 0.5% Tween 20), the blots were incubated with a donkey anti-goat (for ZBP-89) secondary antibody conjugated to horseradish peroxidase (Pierce Biotech) for one hour. After three more washes in TBST, the blot was incubated with SuperSignal West Pico Chemiluminescent Substrate (Pierce Biotech) and exposed to X-ray film.

## Results

Human gingival fibroblasts (HGF) were serum-deprived for 16 hours and then treated with IL-1 (10 ng/ml) and/or IL-4 (10 ng/ml) for 12 hours. ZBP-89 mRNA was measured by real-time PCR. Figure 1 shows a decrease in steady-state levels of ZBP-89 mRNA in response to the pro-inflammatory cytokine IL-1 $\beta$ , but no change in response to the anti-inflammatory IL-4. Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) also inhibits ZBP-89 expression in HGF to a similar extent, and both inflammatory cytokines are effective at doses as low as 0.1 ng/ml (Figure 2). A time course shows that both mRNA and protein expression are inhibited within six hours of treatment with IL-1 $\beta$ , and the levels continue to decrease for at least 24 hours (Figure 3).



**Figure 1** IL-1 inhibits ZBP-89 mRNA expression in HGF. HGF cultures were serum-deprived for 16 hours prior to addition of IL-1 $\beta$  (10 ng/ml) and/or IL-4 (10 ng/ml). Total RNA was harvested 12 hours after cytokine treatment, quantitated by real-time PCR and normalized to levels of GAPDH.

**Notes:** The graph represents data from seven independent experiments performed in triplicate, expressed as mean  $\pm$  SEM. Statistical significance was determined using Student's *t*-test. \*\**p* < 0.01.

**Abbreviations:** GAPDH, glyceraldehyde-3-phosphate dehydrogenase; HGF, human gingival fibroblasts; IL, interleukin; PCR, polymerase chain reaction; SEM, standard error of mean.

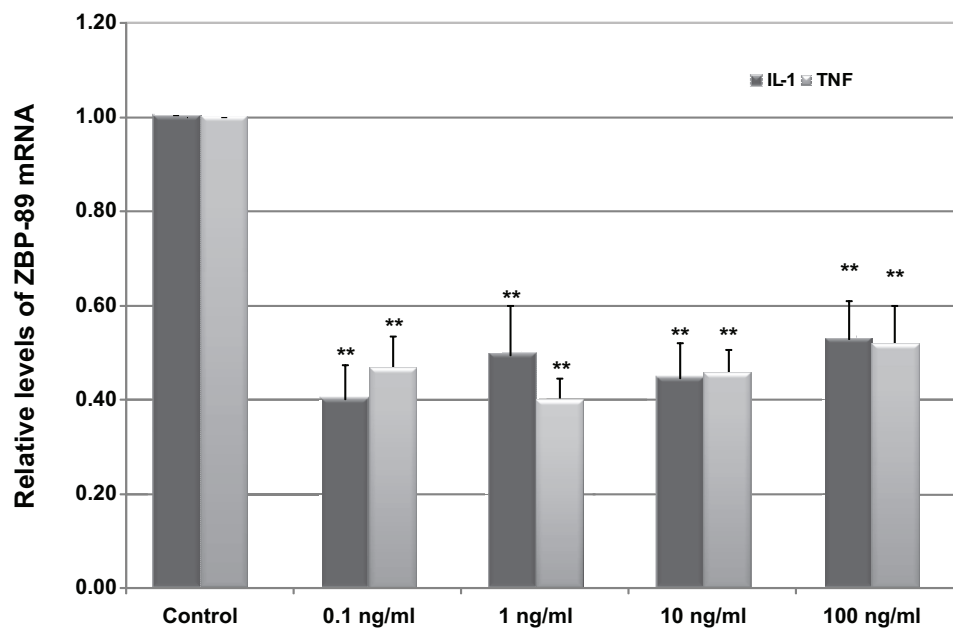
Since there have been some reports of altered responses in fibroblasts isolated from individuals with chronic inflammatory conditions, WI-38 normal human fibroblasts were used to compare responses. Our results (Figure 4) demonstrate a similar decrease in response to IL-1 $\beta$ , no change

in response to IL-4, transforming growth factor- $\beta$  (TGF- $\beta$ ), or EGF. LPS, however, did inhibit ZBP-89 expression, though not as much as IL-1 $\beta$ . Interestingly, TNF did not inhibit ZBP-89 mRNA expression in these normal cells.

## Discussion

Here we report that the expression of ZBP-89 is inhibited by inflammatory cytokines IL-1 $\beta$  and TNF- $\alpha$  in human gingival fibroblasts isolated from patients with severe periodontitis, and by IL-1 $\beta$  and LPS but not TNF- $\alpha$  in WI-38 normal human fibroblasts.

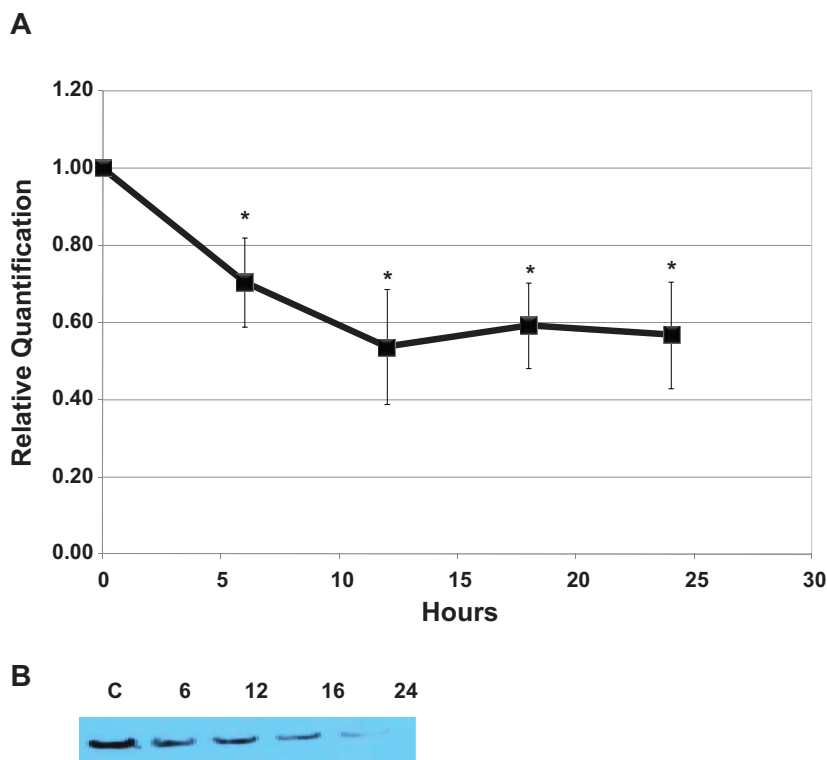
The mechanism of cytokine suppression of ZBP-89 mRNA levels was not determined. Since both mRNA and protein levels were significantly reduced within six hours, it is possible that there is a direct effect on transcription. However, changes in mRNA stability cannot be ruled out. Sequence analysis<sup>21</sup> identified several putative transcription factor binding sites that were well conserved in the promoters of the mouse and human genes, including Sp1, TCF-1, Oct1, NF- $\kappa$ B, MyoD, Ets1, LyF-1, and BERF-1/ZBP-89 itself, but a functional analysis of these elements has not been done. There was evidence of alternative polyadenylation sites in the 3' untranslated region,<sup>21</sup> but no AUUA elements associated with mRNA instability have been noted. In addition to regulation of the levels of ZBP-89 expressed,



**Figure 2** IL-1 $\beta$  and TNF- $\alpha$  inhibit ZBP-89 mRNA expression at low doses. HGF cultures were serum-deprived for 16 hours prior to addition of IL-1 $\beta$  (10 ng/ml) or TNF- $\alpha$  (10 ng/ml). Total RNA was harvested 12 hours after cytokine treatment, quantitated by real-time PCR and normalized to levels of GAPDH.

**Notes:** The graph represents data from five independent experiments performed in triplicate, expressed as mean  $\pm$  SEM. Statistical significance was determined using Student's *t*-test. \*\**p* < 0.01.

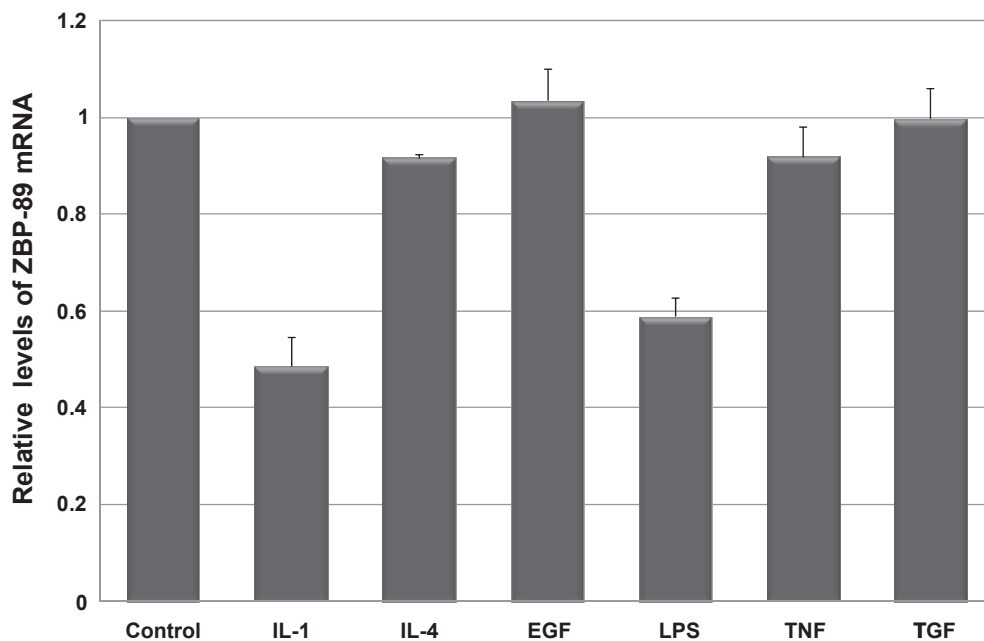
**Abbreviations:** GAPDH, glyceraldehyde-3-phosphate dehydrogenase; HGF, human gingival fibroblasts; IL, interleukin; PCR, polymerase chain reaction; SEM, standard error of mean; TNF, tumor necrosis factor.



**Figure 3** IL-1 $\beta$  inhibits ZBP-89 mRNA expression within six hours. **A)** HGF cultures were serum-deprived for 16 hours prior to addition of IL-1 $\beta$  (10 ng/ml). Total RNA was harvested at the indicated hours after cytokine treatment, quantitated by real-time PCR and normalized to levels of GAPDH. **B)** Immunoblot of whole cell extracts isolated from HGF cultures treated for the indicated times with IL-1 $\beta$  as described above and treated anti-ZBP-89 antibody.

**Notes:** The graph represents data from five independent experiments performed in triplicate, expressed as mean  $\pm$  SEM. Statistical significance was determined using Student's *t*-test. \**p* < 0.05.

**Abbreviations:** GAPDH, glyceraldehyde-3-phosphate dehydrogenase; HGF, human gingival fibroblasts; IL, interleukin; PCR, polymerase chain reaction; SEM, standard error of mean.



**Figure 4** ZBP-89 mRNA is inhibited by IL-1 $\beta$  and LPS, but not by TNF- $\alpha$  in WI-38 cells. WI-38 cell cultures were serum-deprived for 16 hours prior to addition of cytokines/ inflammatory mediator (10 ng/ml). Total RNA was harvested 12 hours after treatment, quantitated by real-time PCR, and normalized to levels of GAPDH.

**Notes:** The graph represents data from two independent experiments performed in triplicate, expressed as mean  $\pm$  SEM.

**Abbreviations:** GAPDH, glyceraldehyde-3-phosphate dehydrogenase; EGF, epidermal growth factor; IL, interleukin; LPS, lipopolysaccharide; PCR, polymerase chain reaction; TNF, tumor necrosis factor; SEM, standard error of mean.

there is also evidence of post-translational regulation of ZBP-89 transcriptional activity by phosphorylation<sup>22</sup> and/or sumoylation,<sup>23</sup> but so far little is known about what kinds of stimuli might regulate these modifications, and in what cellular contexts.

Although ZBP-89 is ubiquitously expressed, it is more abundant in some tissues<sup>6,24,25</sup> and there is evidence of developmental regulation of its expression.<sup>8</sup> In addition, its mRNA has been shown to be modestly induced by retinoic acid<sup>26</sup> as well as TGF- $\beta$  and butyrate.<sup>1,27</sup> Although it has been shown to be over-expressed in certain cancers,<sup>28</sup> it limits cell proliferation, in part through interactions with p53,<sup>29</sup> and appears to have roles in cell differentiation<sup>8,30</sup> and apoptosis.<sup>31</sup> In addition, ZBP-89 has also been proposed to have a protective effect in the resolution of inflammation.<sup>32</sup> Therefore, one might speculate that suppression of ZBP-89 expression by inflammatory cytokines might serve to allow cytokine mediated increases in cellular proliferation, prolong the immune response and/or protect against apoptosis. For example, both IL-1 and TNF have been shown to stimulate ornithine decarboxylase (ODC) expression, but only in cell types in which they are able to stimulate proliferation.<sup>33</sup> It is tempting to speculate that they might do this, at least in part, by inhibiting ZBP-89 repression of ODC expression. On the MMP-3 promoter, decreased levels of ZBP-89 would presumably allow NF- $\kappa$ B to bind unopposed to both the 5T and 6T versions of the polymorphic site, causing both to function as repressor elements *in vivo* (although the 6T would be a more effective repressor element because of a higher affinity for NF- $\kappa$ B). This would help to limit the amount of MMP-3 expressed, and thus reduce pathological tissue remodeling during prolonged inflammation.

It is interesting to note that although TNF- $\alpha$  inhibited ZBP-89 mRNA expression in HGF in a way similar to IL-1 $\beta$ , it failed to do so in WI-38 cells. This suggests that there are cell-type specific differences in the TNF- $\alpha$  pathway as it relates to ZBP-89 expression. It is possible that these differences result from alterations in the HGF caused by chronic inflammation. For example, Rowanpura and colleagues<sup>34</sup> showed that HGF isolated from patients with severe periodontitis differed from normal gingival fibroblasts from healthy donors in their response to prostaglandin E<sub>2</sub>, and that this was a result of a change in receptors from EP<sub>2</sub> and EP<sub>4</sub> in healthy tissue to predominantly EP<sub>1</sub> in diseased tissue. In another study, TNF- $\alpha$  induced proliferation of synovial fibroblasts isolated from patients with rheumatoid arthritis, but failed to do so in normal synovial fibroblasts.<sup>35</sup>

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