Published in final edited form as:
Crit Rev Immunol. 2012 ; 32(2): 127–138.

p120-CATENIN: A NOVEL REGULATOR OF INNATE IMMUNITY AND INFLAMMATION

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Abstract

p120-Catenin is the prototypic member of a subfamily of armadillo repeat domain proteins. Like its structural homologues, β- and γ-catenin, p120-catenin is an essential component of adherens junctions in endothelial cells and other polarized adherent cells. p120-Catenin binds directly to the cytoplasmic domain of cadherin and contributes to the regulation of cell–cell junctional integrity. Studies have demonstrated that p120-catenin plays important roles in cell–cell adhesion, embryonic development, cell proliferation and polarity, tumor cell migration, and cancer progression. However, recent insights have generated an entirely new perspective, suggesting that p120-catenin is implicated in the anti-inflammatory responses in the absence and presence of infection. This review summarizes the present knowledge and recent progress toward elucidating the novel role of p120-catenin in the regulation of innate immunity and inflammation.

Keywords

adherens junctions; Toll-like receptor; neutrophil; nuclear factor-κB; adhesion; cytokines

I. INTRODUCTION

Members of the p120-catenin subfamily include p120-catenin, armadillo repeat protein deleted in Velo-Cardio-Facial syndrome (ARVCF)-catenin, δ-catenin/neural plakophilin-related armadillo repeat protein (NPRAP), and p0071, as well as the more distantly related plakophilins 1–3.[1,2] p120-Catenin (also known as catenin delta-1), a member of the armadillo supergene family, was initially discovered as a substrate for *Src* kinase in 1989.[3] Three years later, a nearly full-length complementary DNA (cDNA) encoding murine p120-catenin was isolated.[4] In 1994, p120-catenin was shown to interact with epithelial (E)-cadherin in NIH 3T3 (murine fibroblast), Madin Darby canine kidney epithelial cells,[5] and HT29 cells.[6] Armadillo repeats mediate specific protein–protein interactions, analogous to the role of *Src Homology 2* (SH2) or ankyrin domains.[4,7] p120-Catenin can be tyrosine phosphorylated in response to platelet-derived growth factor, epidermal growth factor, and colony-stimulating factor 1.[8] p120-Catenin binds the E-cadherin or vascular endothelial (VE)-cadherin cytoplasmic tail at a highly conserved octapeptide sequence (YDEEGGGE)[9] within the juxtamembrane domain.[10,11–18] Mutations of the cadherin juxtamembrane domain have shown that this domain is both necessary and sufficient for recruitment of p120-catenin to adherens junctions,[15] indicating an important role in the regulation of cell–cell adhesion and cell motility.[19] In addition to the regulatory role of cadherin stability, p120-catenin is physically or functionally linked to a wide variety of proteins, including receptor tyrosine kinases (*Src*, Yes, Fer, and Fyn),[20] receptor-like protein tyrosine phosphatase μ,[21] protein-tyrosine phosphatase Src homology phosphatase-1,[22,23] tumor-suppressor adenomatous polyposis coli,[7,14] Rho GTPases,[24–26] transcription regulator

Kaiso,[27–31] and Wnt signaling proteins glycogen synthase kinase 3β (GSK-3β) and axin.[32] These findings unambiguously demonstrated the important roles of p120-catenin in the regulation of cell–cell adhesion, embryonic development, cell proliferation and polarity, tumor cell migration, and cancer progression.[33,34]

Although p120-catenin is best known for its role in cell adhesion, there is growing evidence that p120-catenin functions as an endogenous anti-inflammatory mediator in many tissues and organs.[35,36] Conditional knockout mice for tissue-specific ablation of p120-catenin in the absence of infection exhibited increased inflammatory cell infiltration and production of proinflammatory cytokines.[35,36] p120-Catenin also has a function in regulating innate immunity and sepsis-related inflammation. p120-Catenin expressed in endothelial cells modulates endotoxin-induced lung inflammation through its ability to interfere with Toll-like receptor (TLR) 4 signaling.[37] The focus of this review is to elucidate the role of p120-catenin in the regulation of innate immunity and inflammatory response.

II. STRUCTURAL AND FUNCTIONAL PROPERTIES OF P120-CATENIN

A. The Basic Structure and Isoforms of p120-Catenin

p120-Catenin is an armadillo repeat-containing protein composed of four distinct functional regions (Figure 1). From the N- to C-terminus, these regions include coiled coil, regulatory domain, and armadillo domain containing 10 armadillo repeats and a short C-terminal tail. Owing to alternative splicing and multiple translation initiation codons, multiple p120-catenin isoforms can be expressed from a single gene.[38] In the N-terminal regulatory domains, alternative splicing events leads to the use of four different start codons, resulting in the expression of four main p120-catenin isoforms type 1, 2, 3 or 4, according to the respective ATG used as the translation start site. The relative abundance of each p120-catenin isoform varies among cell types. p120-Catenin isoform 1 is the full-length protein containing a 347-amino-acid N-terminal domain, whereas p120-catenin isoforms 2 and 3 start at amino acids 55 and 102, respectively. In contrast, p120-catenin isoform 4 lacks the N-terminal domain, with only the central armadillo domain, the 10 tandem 42-amino-acid repeats, and the C-terminal domain.[39,40] Alternative splicing events also occur in the C-terminal end, leading to the use of exons A, B, or neither of them. Exon C is rarely inserted within armadillo repeat 6 of p120-catenin. Therefore, various combinations of these N- and C-terminal alternative splicing events result in approximately 32 isoforms of p120-catenin in human.[38,41] In addition, differential posttranslational modifications could further increase the molecular variety of these proteins because they could be phosphorylated on serine/threonine and tyrosine residues by several protein kinases.[42]

p120-Catenin is widely expressed in all cells capable of adhering to other cells, including endothelial and epithelial cells, fibroblasts, macrophages, cardiomyocytes, and neurons,[43] but it is weakly expressed or absent in B and T lymphocytes.[43] The most commonly expressed isoforms are isoforms 1 and 3. Isoform 1 is predominantly expressed in motile cells such as fibroblasts and in epithelial tumors, while isoform 3 is the most abundant isoform in sessile epithelial cells.[40]

B. Interaction Between p120-Catenin and Other Proteins

Association of proteins to p120-catenin takes place through different elements. Two domains of p120-catenin are likely to mediate protein–protein interactions, either directly or indirectly following p120 phosphorylation.[44] Kaiso and cadherin interact with p120-catenin through the central armadillo domain,[45] whereas other cofactors, such as the Fer or Fyn tyrosine kinases[46] and RhoA GTPase,[44,47] bind sequences in the regulatory domain. p120-Catenin phosphorylation occurs not only on tyrosine but also on serine and threonine residues, which are predominantly in the N-terminal domain of the protein.[48,49] p120-

Catenin acts as guanine nucleotide dissociation inhibitor for RhoA[24,50] and also binds Vav2, an guanine nucleotide exchange factor that specifically activate Cdc42 and Rac1,[25] regulating cell–cell adhesion.

p120-Catenin exists in three pools: a membrane-associated cadherin-bound pool,[33,34,44] a soluble, cytoplasmic pool that affects Rho GTPases,[6,15,16,51–53] and a nuclear pool that is thought to associate with the methylation-relevant transcriptional repressor Kaiso.[54] Cadherin-bound p120-catenin on the cell membrane is unable to affect the structure of the actin cytoskeleton, whereas cadherin-unbound p120-catenin in a cytoplasmic pool can interact with Vav2 and possibly other regulators of Rho family activity.[25] Cytosolic p120-catenin inhibits the activity of RhoA by acting as a guanine nucleotide dissociation inhibitor and sequestering RhoA in its inactive form.[24,55] Overexpression of exogenous p120-catenin mainly increases the cytosolic pool of p120-catenin relative to the fraction associated with the membrane.[25] The distribution of p120-catenin between cadherin-bound and cytoplasmic pools may provide a crosstalk mechanism for regulating cadherin-mediated cell–cell junctions and the motile machinery of cells.[25]

C. Regulation of p120-Catenin Expression

p120-Catenin expression is downregulated in human cancers of diverse etiologies, and it correlates closely with poor patient prognosis.[56] Following lipopolysaccharide (LPS) challenge, p120-catenin expression level in the mouse lungs was rapidly decreased. The p120-catenin protein expression was correlated inversely with severity of inflammation.[37] The molecular mechanisms by which p120-catenin is degraded are not exactly clear. Calpain 1 has been shown to mediate the degradation of p120-catenin in ischemic human neuroblastoma SH-SY5Y cells[57] and endothelial cells.[58] Pretreatment of epithelial cells with calpain inhibitor or knockdown of calpain 1 with a specific small interfering RNA (siRNA) prevented mechanical stretch-induced loss of p120-catenin.[59] These results support the notion that calpain-1 may mediate p120-catenin degradation. A recent study indicated that p120-catenin ubiquitination and proteasomal degradation is phosphorylation dependent. The N-terminal region of p120-catenin can interact with destruction-complex proteins (e.g., casein kinase-1α and GSK3β). Like β-catenin, p120-catenin is phosphorylated by casein kinase-1α and GSK3β and degraded through the ubiquitin-proteasome pathway.[32] p120-Catenin was stabilized by the proteasome inhibitor MG132 (carbobenzoxy-Leu-Leu-leucinal) in a dose-dependent manner. Furthermore, p120-catenin ubiquitination was dramatically increased upon its coexpression with HA–ubiquitin in HeLa cells, and it dropped when cells were incubated in the presence of LiCl.[32] These findings suggest the important role of canonical Wnt signaling in the regulation of endogenous p120-catenin expression.

D. The Physiological Functions of p120-Catenin

The physiological functions of p120-catenin are not completely understood. Evidence has accumulated over the past decade that p120 acts as a critical regulator of cell–cell adhesion by stabilizing E-cadherin hemophilic interactions and by maintaining the total level of E-cadherin expression in epithelial cells.[33] p120-Catenin binding to the cytoplasmic domain in juxtamembrane regions via its central armadillo domain prevents the endocytosis and degradation of E-cadherin. Knockout of p120-catenin in mice causes early embryonic lethality, despite the presence of the genome of several potentially redundant p120-catenin family members.[33] Tissue-specific deletion of p120-catenin in mice results in a variety of phenotypes with differing degrees of severity. Ablation of p120-catenin specifically restricted to the gastrointestinal tract is lethal within a few weeks after birth.[39] Conditional knockout mice for endothelial p120-catenin died embryonically beginning at embryonic day 11.5.[60] Mice lacking endothelial p120-catenin exhibit a reduced VE-cadherin and neural

cadherin levels, as well as hemorrhages, decreased microvascular density, reduced pericyte coverage, and disorganized vascular networks in both embryonic and extraembryonic tissues, indicating a crucial role for p120-catenin in vascular development and endothelial function.[60] The conditional knockout of p120-catenin in the salivary gland resulted in disorganized ducts, reductions in E-cadherin levels, and the formation of epithelial masses that followed a cancer-like growth progression.[61] Depletion of p120-catenin specifically in forebrain neuroepithelia resulted in reduced density of neuronal spines and synapses, an effect owing more to the misregulation of Rho GTPases than changes in neural cadherin levels.[62] Epidermal conditional p120-catenin knockout mice displayed a chronic inflammatory response,[35,36] suggesting the intrinsic anti-inflammatory role of p120-catenin.

III. ROLE OF P120-CATENIN IN THE REGULATION OF INNATE IMMUNITY AND INFLAMMATION

The innate immune system is the main, first line of host defense against invading microorganisms in a non-specific manner and relies on a large family of pattern recognition receptors (PRRs), which detect distinct evolutionarily conserved structures on pathogens (known as pathogen-associated molecular patterns) and endogenous stress signals (known as danger-associated molecular patterns). PRRs are expressed not only on a variety of immune cells including macrophages, dendritic cells and B cells but also on nonimmune cells including endothelial and epithelial cells. These PRRs include cell surface- or intracellular compartment-expressed receptors such as the TLRs, intracytosolic receptors such as nucleotide binding domain/leucine-rich repeat receptors (NLRs), C-type lectin receptors (CLRs), scavenger receptors, and a variety of other receptor molecules that recognize danger-associated molecular patterns.[63,64] Activation of PRRs results in initiation of several extracellular activating cascades as well as various intracellular signaling pathways that cause inflammatory responses. Among the PRRs, the TLRs have been studied most extensively. TLRs can recognize diverse pathogens and can generate inflammatory signals to activate innate immune responses.[63]

A. Loss of p120-Catenin Causes Intrinsic Inflammation

Depletion of p120-catenin in conditional knockout mice exhibits an inflammatory response in intestines[65–67] and epidermis[35,36] evidenced by tissue immune cell infiltration and proinflammatory cytokine release. Ultrastructural study indicated that the conditional knockout underlying dermis was infiltrated with immune cells, including lymphocytes, mast cells, granulocytes (neutrophils and eosinophils), and macrophages.[35] There was a significant correlation between p120-catenin loss and increased incidence of inflammatory bowel disease.[65–67]

p120-Catenin regulates inflammatory responses in the skin through regulation of NF-κB activation and immune cell migration in the absence of inflammatory stimuli.[53] p120-catenin null epidermal cells have elevated levels of nuclear NF-κB activity, triggering a cascade of proinflammatory NF-κB targets both *in vivo* and *in vitro*.[47,55] Loss of p120-catenin causes activation of RhoA/Rho-kinase pathway, which may result in NF-κB activation and cytokine production.[47] In human endothelial cells, depletion of p120-catenin expression with a specific siRNA increased transcription-factor promoter reporter activities, adhesion molecule expression, neutrophil adhesion, and extracellular signal-regulated kinase 1/2 signaling.[68] Overexpression of a p120-catenin fusion protein in human umbilical vein and dermal microvascular endothelial cells inhibited neutrophil transendothelial migration.[69] These studies clearly demonstrate that the inflammatory response following p120-catenin loss is cell-autonomous at initial stages, mediated by an intrinsic mechanism that does not appear to rely upon noxious stimuli.

B. Innate Immune Function of p120-Catenin in Response to Endotoxin

Our recent findings have indicated the central role of p120-catenin expression in the regulation of sepsis-induced lung injury.[37] In the mouse lung, p120 was rapidly degraded in response to LPS challenge and the levels of p120 protein expression correlated inversely with the severity of lung inflammation. Depletion of p120 in pulmonary vasculature with a specific siRNA rendered the mice highly sensitive to endotoxin, induced a robust inflammatory response evidenced by neutrophil infiltration into the lung, increased proinflammatory cytokine production (tissue necrosis factor-α and Interleukin-6), pulmonary vascular hyperpermeability, and edema formation. [37] Consistently, deletion of p120-catenin with specific siRNA enhanced LPS-induced an increase in neutrophil adhesion to cultured pulmonary endothelial cells and neutrophil transendothelial migration. In contrast, overexpression of p120-catenin blocked LPS-induced effects.[37] Taken together, these results support the novel concept that endothelial p120 degradation that occurs after endotoxemia is required for the amplification of pulmonary inflammation. Therefore, endothelial p120-catenin may be a critical molecule for endothelial homeostasis, and it acts as a crucial negative regulator of sepsis-induced lung inflammatory injury.

C. Regulatory Role of p120-Catenin in TLR4 Signaling Pathway

1. TLR4 Signaling Pathway—TLR4 is the main LPS receptor, although co-receptors including TLR2 are most likely involved.[70–72] LPS binding to TLR4 initiates myeloid differentiation factor (MyD88)-dependent and -independent signaling pathways to activate inflammatory gene expression (Figure 2).[73–76] Recruitment of the adaptor protein MyD88 initiates the early activation of NF-κB and mitogen-activated protein kinase. In parallel, the MyD88-independent pathway leads to rapid activation of interferon regulatory factor 3 (IRF 3)[77,78] but delayed NF-κB activation. [79] MyD88 promotes association with the IL-1 receptor-associated kinase 4 (IRAK4) and IRAK-1. TNF-associated factor 6 (TRAF6) is recruited to IRAK-1.[73,80–82] The complex IRAK-4/IRAK-1/TRAF6 dissociates from the receptor and then interacts with transforming growth factor-β-activated kinase (TAK1) complex. TAK1 activates an inhibitor of NF-κB (IκB) kinase (IKK), leading to phosphorylation and degradation of IκB, and consequent release of NF-κB.[83,84] Once translocated into the nucleus, NF-κB induces the expression of inflammatory chemokines and cytokines. Mitogen-activated protein kinase-mediated activation of transcription factors activator protein 1 and cAMP response element-binding protein also coordinates the induction of many genes encoding adhesion molecules and inflammatory mediators. In addition to MyD88, TRIF (TIR-domain-containing adaptor protein inducing interferon-β)-mediated MyD88-independent induction of interferon-β activates the expression of interferon-inducible genes such as C-X-C motif chemokine 10.[83]

2. Regulation of TLR4 Signaling by p120-Catenin—Using a genetic approach, we demonstrated that p120-catenin significantly inhibited IκB-α degradation and subsequent activation of NF-κB induced by LPS in lungs and pulmonary microvascular endothelial cells.[37] NF-κB activation occurred in p120 null epidermal cells through stimulation of RhoA in the absence of inflammatory stimuli.[35] However, p120 knockdown alone in mouse pulmonary endothelial cells did not affect NF-κB activation but instead significantly enhanced LPS-induced NF-κB activation,[37] suggesting the important role of endothelial p120 in the modulation of LPS/TLR4-dependent NF-κB signaling.

Following LPS-induced TLR4 activation, MyD88 is recruited to the membrane by interaction of its TIR domain with the analogous domain in TLR4. MyD88 binds to IRAK-4 and promotes activation (phosphorylation) of critical IRAK-1 residues by IRAK-4.[85] Upon activation and modification, IRAK-1 dissociates from the receptor complex and associates with TRAF6 to trigger downstream signaling pathways, including the activation of NF-κB

and the induction of inflammatory cytokines.[86] The kinase activity of IRAK-4 is required for the recruitment of IRAK-1 to the receptor complex and for the activation and subsequent degradation of IRAK-1 protein. [87] In pulmonary endothelial cells transfected with a scrambled siRNA, we demonstrated that LPS induced association of MyD88 and TLR4, downstream activation of IRAK4, and subsequent degradation of IRAK-1. Importantly, the increase in TLR4 signaling was further augmented by p120-catenin depletion with a specific siRNA, whereas overexpression of p120-catenin inhibited TLR4 signaling.[37] Although the molecular mechanism(s) by which p120 physically regulates the interaction between MyD88 and TLR4 remains unknown, our study clearly demonstrates that p120 functions as a "negative regulator" of LPS/TLR4-mediated NF-κB activation.[37]

IV. CONCLUDING REMARKS

Studies have greatly expanded our understanding of the functions of p120-catenin during the past two decades. p120-Catenin is primarily an adherens junction-associated protein that regulates cell-cell adhesion via controlling cadherin function and stability. It is now known that p120-catenin participate in a plethora of functions in cells, including cell–cell adhesion, embryonic development, cell proliferation and polarity, tumor cell migration, cancer progression, and anti-inflammatory effects. Despite significant progress in understanding the role of p120-catenin in the development of inflammation, our knowledge is far from complete with regard to the cellular and molecular mechanisms of p120-catenin in the regulation of innate immunity. Studies from conditional knockout mice and cells show that ablation of p120-catain induces inflammatory responses evidenced by immune-cell infiltration, proinflammatory cytokine release, and disruption of cell–cell barrier in the absence of noxious stimuli. It seems likely that p120-catenin is an endogenous anti-inflammatory molecule. We do not yet have a full understanding of whether the inhibitory effect of p120-catenin on inflammation is mainly due to its direct action on cell homeostasis or is secondary to its regulatory role in cell–cell barrier function. Especially in the presence of bacterial infection such as sepsis, how p120-catenin regulates different inflammatory signaling pathways needs further investigation. Finally, we must be aware that most of the data on the role of p120-catenin in inflammation discussed herein, though fascinating, are based on studies commonly using conditional knockout or germ-free mice. It will be important to explore their relevance in human biology.

Acknowledgments

This work was supported by NIH NHLBI grants to Guochang Hu. The project is titled "Role of p120-catenin in sepsis-induced lung injury" (ID No. 5R01HL104092). This research was support by the American Heart Association (Scientist Development Grant No. 0730331N). The author thanks Zhibo Yan and Yu Sun for drafting Figures.

ABBREVIATIONS

E-cadherin	epithelial cadherin
GSK-3β	glycogen synthase kinase 3β
IκB	inhibitor of NF-κB
IKK	IκB kinase
IRF 3	interferon regulatory factor 3
IRAK-1 and IRAK-4	interleukin-1 receptor-associated kinase 1 and 4
LPS	lipopolysaccharide

MyD88	myeloid differentiation factor
NF-κB	nuclear factor-κB
PRRs	pattern recognition receptors
siRNA	small interfering RNA
TLR	Toll-like receptor
TAK1	transforming growth factor-β-activated kinase 1
TRAF6	TNF receptor-associated factor 6
TRIF	TIR-domain-containing adaptor protein inducing interferon-β
VE	vascular endothelial

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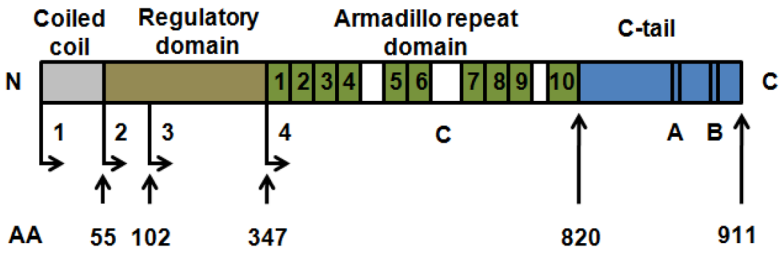

FIGURE 1.
The structure of p120-catenin.

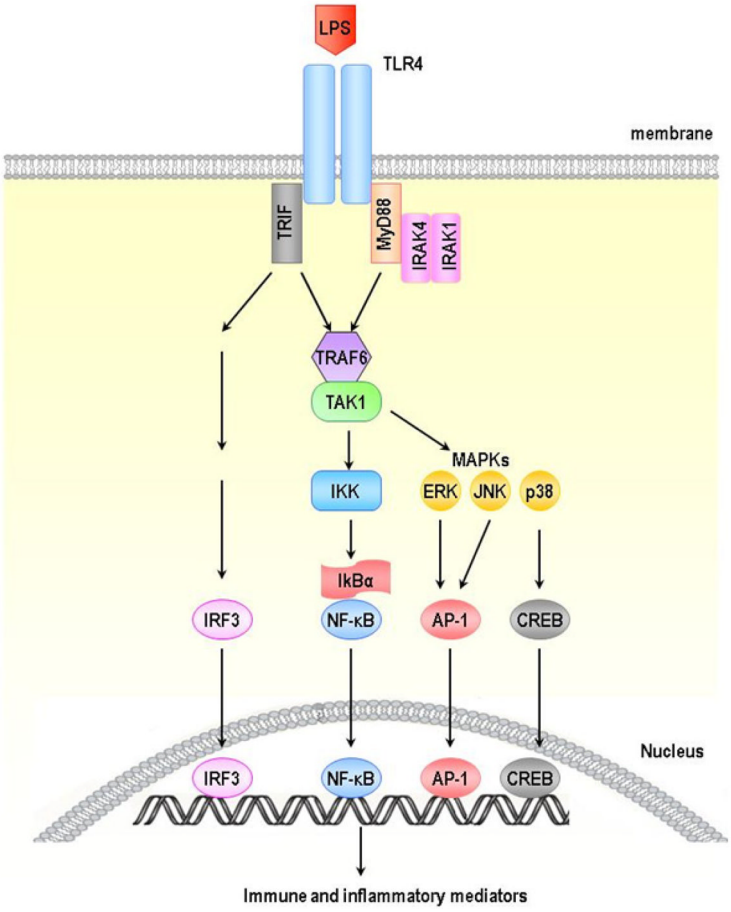

FIGURE 2.

TLR4 signaling pathways regulating inflammation. Abbreviations: AP-1, activator protein 1; cAMP response element-binding protein; ERK, extracellular-signal-regulated kinases; IκB, inhibitor of NF-κB; IKK, IκB kinase; IRF 3, interferon regulatory factor 3; IRAK-1 and IRAK-4, interleukin-1 receptor-associated kinase 1 and 4; JNK, Jun N-terminal protein kinase; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MyD88, myeloid differentiation factor; NF-κB, nuclear factor-κB; TLR, Toll-like receptor; TAK1, transforming growth factor-β-activated kinase 1; TRAF6, TNF receptor-associated factor 6; TRIF, TIR-domain-containing adaptor protein inducing interferon-β.