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R&D Systems Cytokine Bulletin
2008 | Issue 2

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INSIDE

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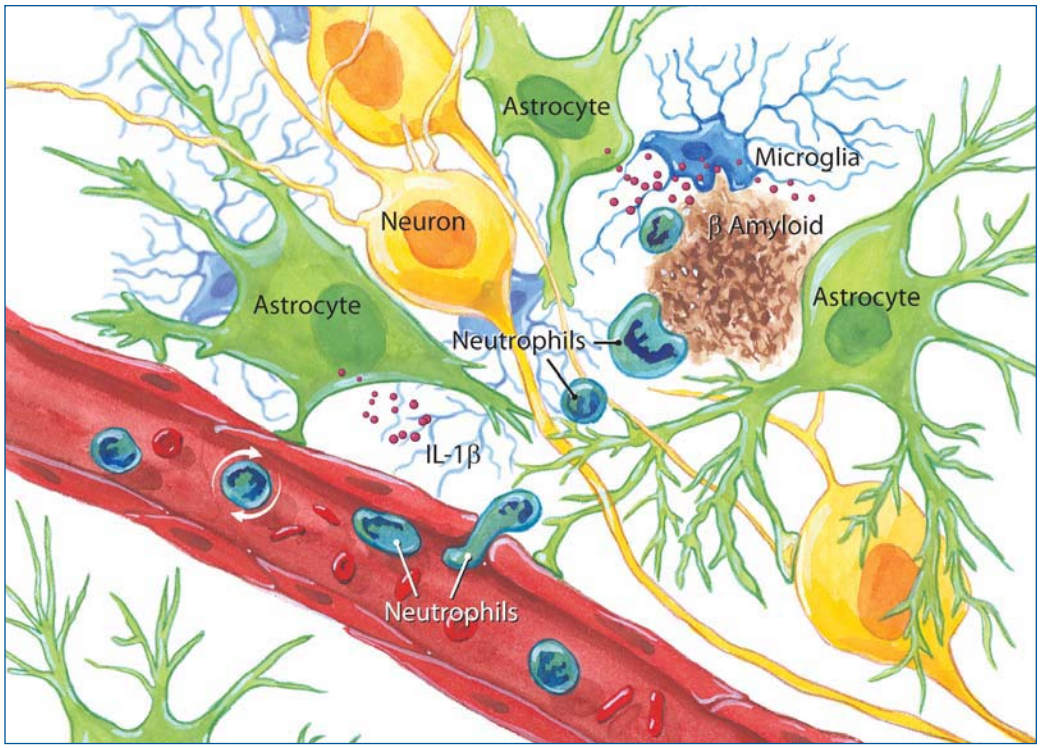


FIGURE 1 β-amyloid plaques induce neuroinflammation as characterized by glial activation and elevation in local pro-inflammatory cytokine production. Recent experiments have reported that transgenic overexpression of human interleukin-1β restricted to the mouse hippocampus is associated with neutrophil recruitment and increased clearing of plaques, highlighting a benefit of the neuroinflammatory response.[13,14]

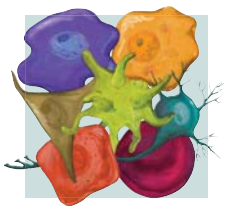
Chronic IL-1β-induced Neuroinflammation

Is it Really that Bad?

The inflammatory response is an early, non-specific immune reaction to tissue damage or pathogen invasion. Originally described as *rubor*, *calor*, *tumor*, and *dolor* (redness, heat, swelling, and pain) by Celsus in 1600,[1] we now know these characteristics of inflammation are due to increased vascular permeability accompanied by a flux of cytokine-releasing phagocytic cells to the site of injury. Usually the inflammatory event is self-limiting as delayed endogenous release of anti-inflammatory molecules limits the duration of pro-inflammatory cytokine action. However, persistence of an antigen (foreign or self) leads to sustained and clustered macrophage activation, a hallmark of chronic inflammation. In addition to cytokines and microbicidal agents that lead to pathogen clearance and tissue repair, the activated macrophages secrete proteolytic enzymes, reactive oxidative species, and secondary intermediates that can cause damage to healthy tissue.[1-4] The numerous diseases associated with chronic inflammation suggest that this lack of resolution may switch the inflammatory response from protective to destructive.

Inflammation of the central nervous system (CNS) is of particular interest since the normal mammalian CNS is considered "immunoprotected" with relatively few resident immune cells and a highly specific blood-brain barrier (BBB). Pattern recognition receptors expressed primarily on microglia, the resident macrophages of the brain, are the initial responders to tissue insult or damage. In concert with astrocytes, reactive microglia produce numerous molecules to recruit other glial cells and peripheral immune cells to the site of injury.[5] Increased glial activation, pro-inflammatory cytokine concentration, BBB permeability, and leukocyte invasion are common events following brain injury and have been documented in neurodegenerative diseases. One key player that is believed to drive this neuroinflammatory process is interleukin (IL)-1β, a pro-inflammatory cytokine that is upregulated in Alzheimer's disease (AD), Parkinson's disease, multiple sclerosis, and other neurodegenerative disorders.[6-8]

Continued on page 5



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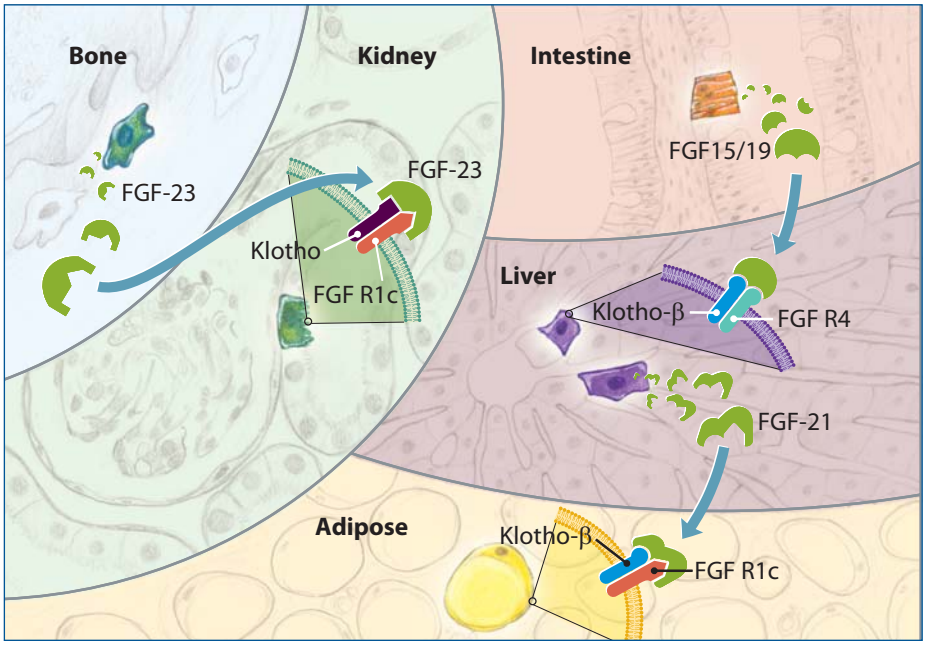
Klotho Proteins: Novel Cofactors for Endocrine FGFs

The fibroblast growth factor (FGF) superfamily includes 22 secreted proteins that all participate in heparan sulfate (HS)-dependent signaling through a group of four FGF receptors and their splice variants. Except for one subfamily, all FGFs exhibit high-affinity binding to heparans and HS, and thus exert paracrine control in areas adjacent to their secretion. Only the FGF-19 subfamily, including FGF-21, FGF-23, and FGF-19 in humans and the mouse FGF-19 equivalent, FGF-15, acts in an endocrine fashion.[1] Although they also are dependent on HS for signaling, they bind these molecules with low affinity and are thus able to circulate more freely than other FGFs. Since they and their FGF receptors are broadly present, tissue specificity of their actions has been somewhat of a mystery. However, recent studies provide a possible explanation. Each of these FGF-19 family members has been shown to require cofactors from the Klotho family of transmembrane proteins. Klotho proteins effectively convert the interacting FGF receptors to receptors specific for select FGF-19 members.[1-3]

Klotho proteins appear to coordinate the complex of HS and FGF Rs with FGF-19 members to provide tissue specificity to these interactions.[1] For example, FGF-19 is produced by intestinal epithelia in response to food intake, but has its activity in the liver where both Klotho-β and FGF R4 are expressed. There it completes a feedback loop to downregulate two key genes in the bile acid synthase pathway, cholesterol 7α-hydroxylase (Cyp7a1) and sterol 12α-hydroxylase (Cyp8b1).[3-5] Similarly, FGF-23, while produced in the bone, acts instead on Klotho- and FGF R1c-expressing kidney cells. This interaction enables FGF-23 to have a profound negative regulatory effect on 1α-hydroxylase, the rate-limiting enzyme in the synthesis of $1,25(OH)_2D_3$ (vitamin D), and thus affect calcium and phosphorus homeostasis.[2,6] While FGF-21 and Klotho-β are both expressed in the liver, expression of Klotho-β with FGF R1c in adipose tissue instead confers FGF-21 activity there. Its action in adipocytes enhances production of the GLUT1 transporter, stimulating lipolysis and glucose uptake in the fasting state.[3,7]

The effect of Klotho proteins on energy metabolism and aging is a fascinating and still unfolding story. Because its disruption produces a premature aging-like syndrome, Klotho is named for a Greek goddess, one of the three Fates, who "spins the thread of life."[8] By mechanisms not entirely understood, the aging symptoms of Klotho-deficient mice can be partially ameliorated by restoring negative control over systemic vitamin D activity.[2] Klotho-β may also participate in the control of aging by acting as a cofactor to mediate the key effects of FGF-21 on metabolic changes occurring during calorie restriction, a phenomenon known to prolong lifespan.[9] Klotho participates in other anti-aging activities that may or may not involve FGF-19 family members. It downregulates insulin and IGF signaling and increases endothelial cell resistance to oxidative stress, both of which may also contribute to longevity.[10,11] Recently, Klotho has been identified as a Wnt antagonist that potentially limits Wnt-mediated cellular senescence.[12] Some of these effects appear to involve interaction of proteolytically released, soluble Klotho with a receptor yet to be identified.[10-12]



Klotho family members increase the affinity of FGF-19 family members for their receptor/heparan sulfate combination. Limited expression and combination of Klothos and FGF receptors allows tissue specificity of FGF activity.

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The Multiple Functions of IL-33

IL-33 was independently described by three different research groups interested in distinct biological topics. Onda *et al.* identified DVS27 as a protein that is upregulated in vasospastic cerebral arteries.[1] Baekkevold *et al.* identified NF-HEV as a nuclear factor in the endothelial cells of high endothelial venules.[2] Schmitz *et al.* identified IL-33 as an interleukin-1 family cytokine.[3] DVS27, NF-HEV, and IL-33 all refer to the same multi-functional protein that is expressed primarily by endothelial and smooth muscle cells in the vasculature and airway.[3,4] IL-33 is upregulated by inflammatory stimulation in these cells, as well as keratinocytes and dermal fibroblasts, and by mechanical strain in cardiac fibroblasts.[1,5,6]

IL-33 is synthesized as a 270 amino acid protein in humans and contains an N-terminal nuclear localization signal (NLS), a helix-turn-helix (HTH) motif, and a C-terminal region with structural homology to IL-1 family cytokines. It can be cleaved *in vitro* by caspase-1 to generate an 18 kDa C-terminal fragment, which serves as a cytokine.[3,5] The fate of the released N-terminal fragment has not yet been described. Full length IL-33 localizes to the nucleus where it associates with heterochromatin and mitotic chromosomes.[1,2,5] Both of these interactions are mediated by the HTH motif but not the NLS.[5] IL-33 functions in this context as a transcriptional repressor, although particular target genes have not been identified.[5]

The C-terminal fragment of IL-33 is the only cytokine that has been shown to bind the receptor ST2L.[3,7-9] The IL-33/ST2L complex subsequently associates with IL-1R AcP to enable IL-33-dependent activation of NFκB.[3,10] IL-1R AcP is a shared signaling subunit that also associates with IL-1 RI and IL-1 R6. Extracellular IL-33 promotes Th2-biased immune responses, resulting in eosinophilia and allergic inflammation. In Th2 cells, it upregulates the production of IL-4, IL-5, and IL-13 as well as ST2L.[3,10] In mast cells, it cooperates with TSLP in inducing the production of several cytokines and chemokines but does not trigger mast cell degranulation or eicosanoid production.[7]

Alternative splicing of ST2L generates ST2, a soluble decoy receptor that is elevated in the serum of asthma and heart failure patients.[6,8] ST2 association with IL-33 blocks ST2L-dependent signaling and the immunological and cardiac effects of IL-33.[6-8] The IL-33/ST2L system has a distinct role in the heart. IL-33 counteracts cardiac myocyte hypertrophy, which is induced by angiotensin II or phenylephrine.[6] This cardioprotective effect is reliant on ST2L-mediated signaling.[6] In parallel to the induction of IL-33 in cardiac fibroblasts, ST2 is induced in cardiac myocytes by mechanical stress.[6]

IL-33 shows similarities to IL-1α and HMG-B1 in that it exhibits both nuclear and extracellular functions.[4] Unlike those factors, however, little is known about the regulation of the full length and processed forms of IL-33. Further investigations will likely uncover relationships between its transcriptional targets, chromosome binding, immune and cardiac functions, and potential signaling crosstalk induced by other cytokines that utilize IL-1R AcP.

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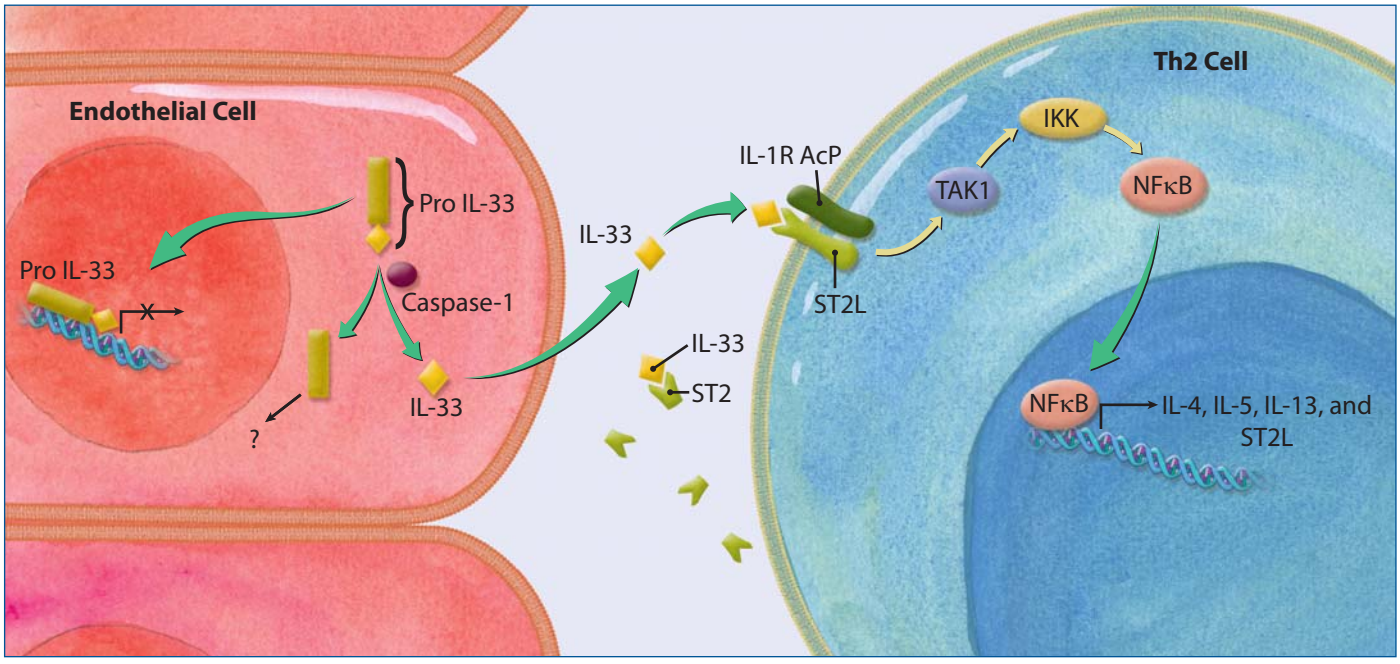

Full length IL-33 (Pro IL-33) localizes to the nucleus where it inhibits gene transcription. The C-terminal cytokine-like fragment of IL-33 is released and binds ST2L. Ternary complexes of IL-33/ST2/IL-1R AcP transduce signals that result in increased expression of proteins involved in allergic inflammation.

Glypicans in Cancer

Proteoglycans (PGs) are glycoproteins that contain long, covalently-linked unbranched chains of repeating disaccharides. HSPGs, proteoglycans with heparan sulfate (HS) glycosaminoglycan (GAG) chains, are abundant components of cells and the extracellular matrix (ECM) and as such serve diverse roles in development and pathophysiology.[1] HSPGs act as signaling co-receptors for growth factors and morphogens, regulate the stability and distribution of signaling molecules in the ECM and chemokine gradients at sites of injury, modulate cell adhesion and motility, and affect intracellular membrane trafficking.[2] There are three classes of HSPGs: the secreted extracellular matrix proteoglycans, the transmembrane syndecans, and the GPI-linked glypicans.[1,2] In mammals, six glypicans (GPC1-6) have been identified. All have a 60-70 kDa protein core, are glycosyl phosphatidylinositol (GPI)-linked to the cell membrane, and due to their globular structure are restricted to HS-type GAG attachments.[1-3]

Since glypicans act as co-receptors by facilitating the formation of ligand-receptor complexes and effectively lowering the required concentration of ligand, it is not surprising that they are expressed in the tumor environment.[4] Glypican-1, -3 and -5 have all been associated with the tumorigenic process, mostly by affecting growth factor signaling and cell proliferation. GPC1 shows increased expression in human gliomas and glioma-derived cell lines, and acts by enhancing fibroblast growth factor (FGF) basic signaling and mitogenesis.[5] Likewise, in pancreatic and breast cancer cells GPC1 is over-produced, and affects regulation of FGF basic and heparin-binding EGF-like growth factor (HB-EGF) signaling.[6,7] Antisense depletion of GPC1 in pancreatic cancer cells also reduces their ability to form tumors *in vivo*.[8] Another example of glypican-promoted proliferation of tumor cells involves GPC5. Its upregulation has a strong association with the appearance and increased cell proliferation of rhabdomyosarcoma, a malignant skeletal muscle tumor. The mechanism involves GPC5-mediated activity of FGF basic, hepatocyte growth factor (HGF), and Wnt-1.[9]

Interestingly, the role glypican-3 plays in tumorigenesis is less straightforward. On the one hand, GPC3 is overexpressed in and promotes the growth of hepatocellular carcinoma.[10,11] It does so by attenuating FGF basic and bone morphogenetic protein-7 (BMP-7) signaling, yet stimulating canonical Wnt signaling.[10,11] On the other hand, knock-down of GPC3 function in HepG2 hepatoma cells promotes their growth, and GPC3 is frequently silenced in mesotheliomas, ovarian cancer, and breast cancer cell lines.[3,12] A further indication that GPC3 may act as an inhibitor of cell proliferation comes from the clinical characteristics of Simpson-Golabi-Behmel syndrome, which renders GPC3 non-functional. Patients display a variety of abnormalities, including pre- and postnatal overgrowth and a susceptibility to certain malignancies.[13]

While negatively charged sulfate groups on HS chains interact with basic amino acids on ligands, it appears that the simple immobilization of growth factors on HS is insufficient to fully explain the role of glypicans in growth factor-mediated signal transduction. For instance, the location and amount of sulfation impacts the ability of FGF Receptor 2c to interact with heparan sulfate. This requires the presence of both 2-O- or 6-O-sulfated residues.[14] There is also evidence that the HS chains are not required for all proteoglycan activities and that the protein core interacts with growth factors independently of HS chains.[1,3] In addition, glypicans can be secreted, and perhaps act through a different mechanism than membrane-bound forms.[3] Nonetheless, proteoglycan regulation of growth factor sequestration and signaling makes glypicans (and other glycans) attractive targets for cancer therapeutics.[4]

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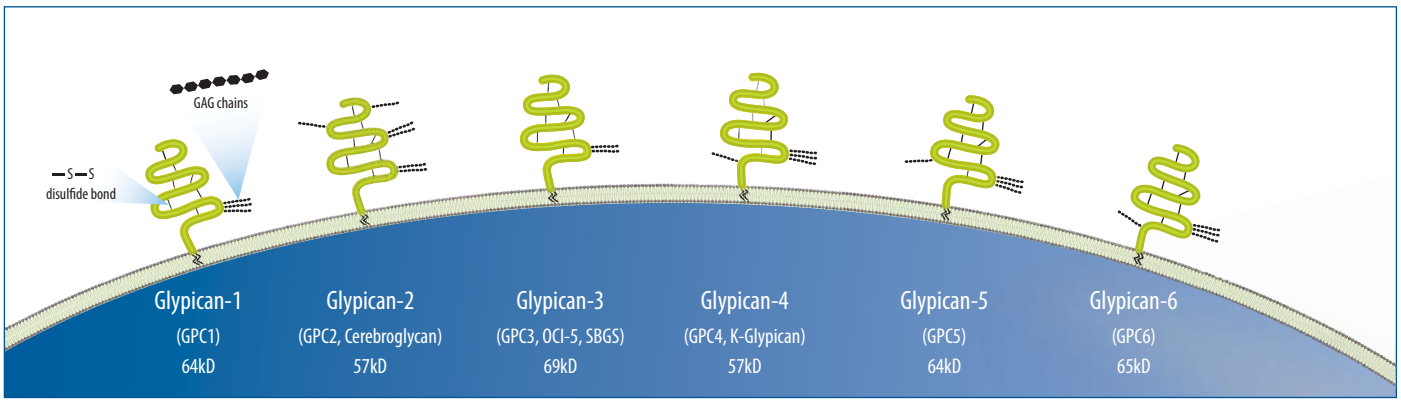

Figure 1. The six members of the vertebrate glypican family share a characteristic structure. Glypicans are anchored to the cell surface via a GPI linkage, have a conserved pattern of 14 cysteine residues, which contribute to intramolecular disulfide linkages, and display GAG attachment sites predominantly near the membrane. Alternative names and molecular weight of the core proteins are also indicated. (Figure is adapted from references 15 &16).

IL-1β signals through the type I IL-1 receptor/IL-1 accessory protein complex, leading to NFκB-dependent transcription of pro-inflammatory cytokines [tumor necrosis factor (TNF)-α, IL-6, and interferons] and neutrophil-recruiting chemokines (CXCL1 and CXCL2) in glia.[9] IL-1β also stimulates production of tau and synaptophysin in neurons, two proteins associated with AD plaques.[10] Whether chronic IL-1β elevation contributes to, or is a consequence of, brain pathology is difficult to determine due to the typical presence of both neuroinflammation and tissue damage upon post-mortem analysis. Animal models of experimental brain injury suggest that IL-1β-mediated leukocyte recruitment and other inflammatory events lead to neuronal cell death; however, few models incorporate long-term expression of this cytokine.[11,12]

To better understand the role of IL-1β in chronic neuroinflammation, Shaftel and colleagues have described a transgenic mouse, IL-1β^{XAT}, that utilizes the *Cre/Lox* system to initiate temporal and spatial expression of human IL-1β in the mouse brain.[13] Unilateral induction of IL-1β gene expression in the hippocampus, a neural region critical for learning and memory, initiates a robust localized inflammatory response consisting of glial activation and inflammatory gene expression (IL-1α, IL-1β, IL-6, TNF-α) that is present up to 10 months following intrahippocampal Cre recombinase injection.[14] As predicted by the expression of chemokines CCL2/MCP-1, CXCL1/KC, and CXCL2/MIP-2, hippocampal IL-1β overexpression also stimulates localized leukocyte migration composed of CD4$^+$CD8$^+$ T cells, dendritic cells, and macrophages that is accompanied by BBB leakage. This migration is dependent on the chemokine receptor CXCR2. The number of CXCR2$^+$ neutrophils remains elevated one year later, re-affirming the IL-1β^{XAT} mouse as a suitable model of chronic neuroinflammation and leukocyte infiltration. However, in contrast to numerous studies implicating neutrophil invasion as a factor in neuronal death,[15] IL-1β^{XAT} mice show no evidence of neuronal cell loss or architectural compromise in the hippocampus at two months post-IL-1β induction. Although surprising, this result may simply suggest that sustained and elevated IL-1β in a normal brain by itself is not harmful; rather, IL-1β may be an accomplice under the influence of other existing factors.

Since the suggestion that rheumatoid arthritis patients treated with non-steroidal anti-inflammatory drugs (NSAIDs) have a lower incidence of Alzheimer's disease (AD),[16] chronic neuroinflammation has been implicated in the stereotypical morphology of β-amyloid plaques and fibrillary tangles found in AD.[17] To address the impact of IL-1β in the face of AD-associated pathology, Shaftel *et al.* crossbred the IL-1β^{XAT} mice with APP/PS1 mice, a transgenic model of AD characterized by accelerated plaque development.[12] Despite previous brain injury studies reporting exaggerated damage in the presence of IL-1β,[18] brains from APP/PS1 mice expressing the IL-1β^{XAT} transgene show decreased β-amyloid plaque frequency and load in the hippocampus. Further analysis of plaque-associated microglia reveals an increase in the number of overlapping microglia, suggesting an enhancement of microglia's phagocytic clearing of amyloid.[19] These results suggest a beneficial role for IL-1β-mediated events in the AD brain. Furthermore, this study provides insight on the lack of clinical benefit of anti-inflammatory treatment in AD patients,[20] drawing a distinction between the role of neuroinflammation in the development of β-amyloid plaques versus being a consequence of these plaques.

In addition to identifying their presence in neurological disorder, understanding the expression of inflammatory molecules with respect to time and context of other biological and pathological events will be critical to maximizing the benefit of neuroinflammation while minimizing its potential harm.

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Society for Developmental Biology
Philadelphia, PA .....July 26-30, 2008

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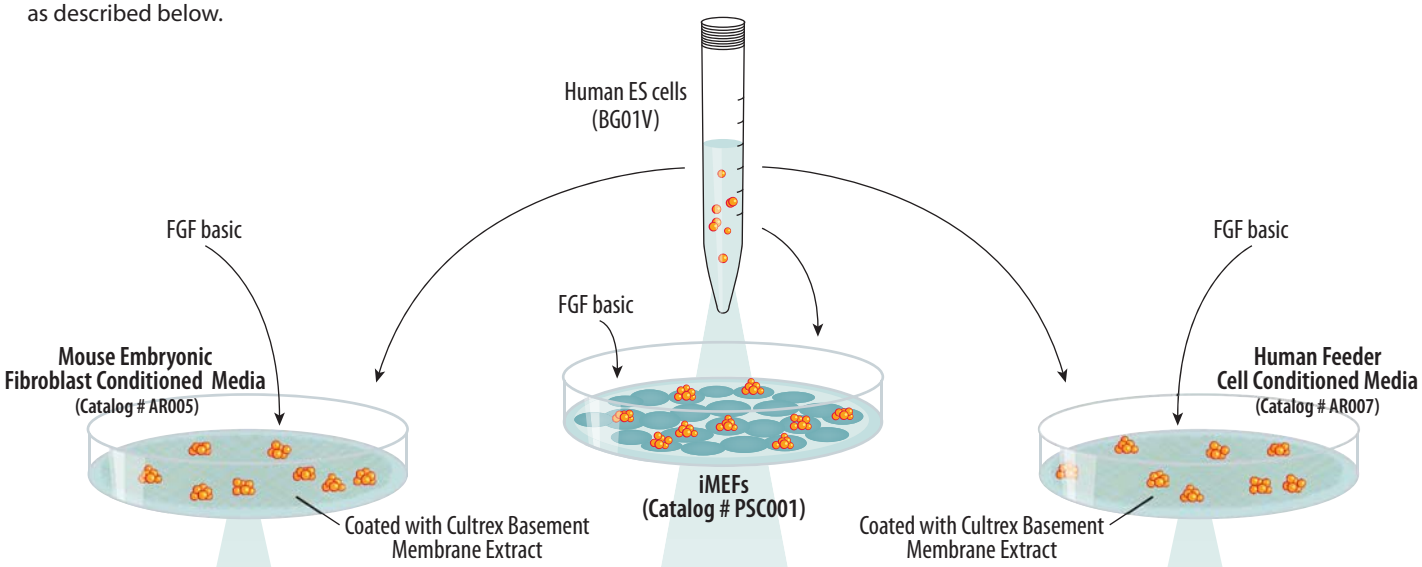
Washington, DC.....July 27-31, 2008

TECHNICAL NOTE: **Culturing Human Embryonic Stem Cells**

R&D Systems offers three ways to support embryonic stem (ES) cell growth and maintain ES cell pluripotency. To culture ES cells, choose from irradiated Mouse Embryonic Fibroblast (iMEF) feeder cells, or feeder-free culture with conditioned media from mouse embryonic feeder cells or from human feeder cells. All three methods are tested for their ability to support growth of the BG01V human ES cell line and are validated by verifying proliferation rates and expression of the pluripotency markers Oct3/4, SSEA-4, SOX2, and Nanog. These reagents may be used in conjunction with Cultrex® Basement Membrane Extract (Catalog # 3433-005-01) and/or FGF basic (Catalog # 233-FB or # 4114-FC) as described below.



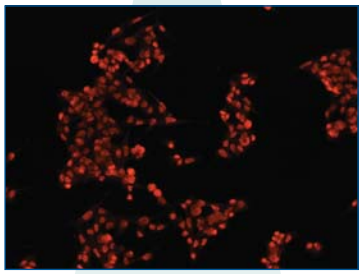


Figure 1. Pluripotency Marker Oct3/4 in Human Embryonic Stem Cells. BG01V cells were cultured using Mouse Embryonic Fibroblast Conditioned Media (Catalog # AR005) for three passages and then fixed and stained with anti-human Oct3/4 polyclonal antibody (Catalog #AF1759) followed by NorthernLights™ 557-conjugated anti-goat IgG secondary antibody (Catalog # NL001).

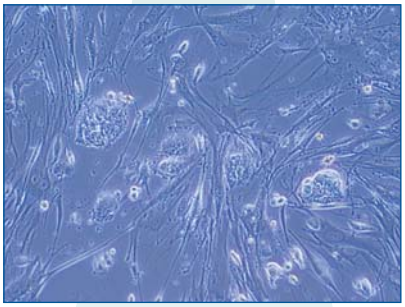


Figure 3. Human Embryonic Stem Cells Grown on iMEF Feeder Cells. Irradiated Mouse Embryonic Fibroblasts (iMEF; Catalog # PSC001) were used to support the undifferentiated expansion of BG01V human embryonic stem cell colonies.

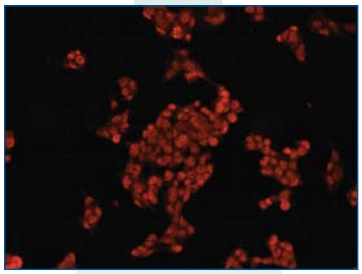


Figure 5. Pluripotency Marker Nanog in Human Embryonic Stem Cells. BG01V cells were cultured using Human Feeder Cell Conditioned Media (Catalog # AR007) for three passages and then fixed and stained with anti-human Nanog polyclonal antibody (Catalog # AF1997) followed by NorthernLights 557-conjugated anti-goat IgG secondary antibody (Catalog # NL001).

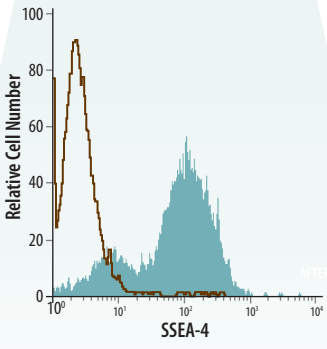


Figure 2. Detection of SSEA-4 in Human Embryonic Stem Cells by Flow Cytometry. BG01V cells cultured in Mouse Embryonic Fibroblast Conditioned Media (Catalog # AR005) were stained using PE-conjugated mouse/human SSEA-4 monoclonal antibody (Catalog # FAB1435P; filled histogram) or PE-conjugated mouse IgG_3 isotype control (open histogram).

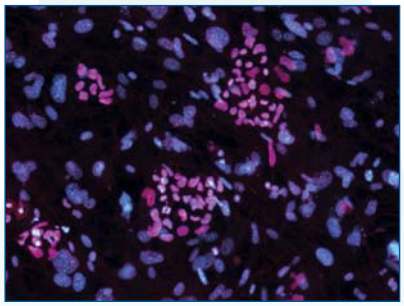


Figure 4. Pluripotency Marker SOX2 in Human Embryonic Stem Cells. BG01V cells were cultured on iMEF (Catalog # PSC001) feeder cells for three passages and then fixed and stained with anti-human SOX2 polyclonal antibody (Catalog # AF2018) followed by NorthernLights 557-conjugated anti-goat IgG secondary antibody (Catalog # NL001; red) and couterstained with DAPI (blue).

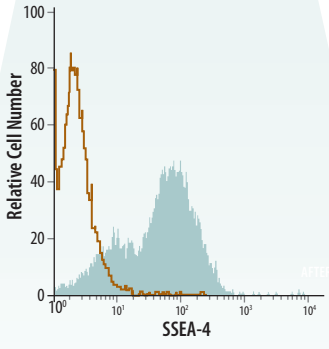


Figure 6. Detection of SSEA-4 in Human Embryonic Stem Cells by Flow Cytometry. BG01V cells cultured in Human Feeder Cell Conditioned Media (Catalog # AR007) were stained using PE- conjugated anti-mouse/human SSEA-4 monoclonal antibody (Catalog # FAB1435P; filled histogram) or PE-conjugated mouse IgG_3 isotype control (open histogram).

RECENT CITATIONS: **R&D Systems Products in Allergy & Asthma**

1. Joubert, P. *et al.* (2008) Expression and regulation of CCR1 by airway smooth muscle cells in asthma. J. Immunol. **180**:1268.

   Human CCL3/MIP-1α Biotinylated Fluorokine® Kit (Catalog # NFLD0)
   Sample: Human primary airway smooth muscle cells
   Application: Receptor detection by flow cytometry

   Human CCR1 Monoclonal Antibody (Catalog # MAB145)
   Sample: Human lung
   Application: Immunohistochemistry

   Recombinant human IFN-γ (Catalog # 285-IF)
   Sample: Human primary airway smooth muscle cells
   Application: Bioassay - effect on CCR1 expression

   Recombinant human IL-4 (Catalog # 204-IL)
   Sample: Human primary airway smooth muscle cells
   Application: Bioassay - effect on CCR1 expression

   Recombinant human IL-13 (Catalog # 213-IL)
   Sample: Human primary airway smooth muscle cells
   Application: Bioassay - effect on CCR1 expression

   Recombinant human TNF-α (Catalog # 210-TA)
   Sample: Human primary airway smooth muscle cells
   Application: Bioassay - effect on CCR1 expression

2. Wang, T.N. *et al.* (2007) The polymorphisms of Eotaxin-1 and CCR3 genes influence on serum IgE, Eotaxin levels and mild asthmatic children in Taiwan. Allergy **62**:1125.

   Human CCL11/Eotaxin Quantikine® ELISA Kit (Catalog # DTX00)
   Sample: Human plasma
   Application: ELISA

3. Matsumoto, K. *et al.* B7-DC induced by IL-13 works as a feedback regulator in the effector phase of allergic asthma. Biochem. Biophys. Res. Commun. **365**:170.

   Mouse IL-13 Quantikine ELISA Kit (Catalog # M1300CB)
   Sample: Mouse bronchoalveolar lavage fluid
   Application: ELISA

   Recombinant Mouse IL-13 Rα 2/Fc Chimera (Catalog # 539-IR)
   Sample: Mouse
   Application: *in vivo*

   Recombinant Mouse GM-CSF (Catalog # 415-ML)
   Sample: Mouse bone marrow-derived mononuclear cells
   Application: Bioassay - dendritic cell generation

   Recombinant Mouse IL-5 (Catalog # 405-ML)
   Sample: Mouse bone marrow-derived dendritic cells
   Application: Bioassay - dendritic cell maturation

4. Monick, M.M. *et al.* (2007) Respiratory syncytial virus synergizes with the Th2 cytokines to induce optimal levels of TARC/CCL17. J. Immunol. **179**:1648.

   Human IL-4 DuoSet® ELISA (Catalog # DY204)
   Sample: Human A549 lung adenocarcinoma cell supernates
   Application: ELISA

   Human IL-13 DuoSet ELISA (Catalog # DY213)
   Sample: Human A549 lung adenocarcinoma cell supernates
   Application: ELISA

   Human CXCL10/IP-10 DuoSet ELISA (Catalog # DY266)
   Sample: Human A549 lung adenocarcinoma cell supernates
   Application: ELISA

   Human CCL17/TARC DuoSet ELISA (Catalog # DY364)
   Sample: Human A549 lung adenocarcinoma cell supernates
   Application: ELISA

5. deOliveira, A.P. *et al.* (2007) Cellular recruitment and cytokine generation in a rat model of allergic lung inflammation are differentially modulated by progesterone and estradiol. Am. J. Physiol. Cell Physiol. **293**:C1120.

   Rat IL-1β Quantikine ELISA Kit (Catalog # RLB00)
   Sample: Rat bronchoalveolar and bone marrow lavage fluids
   Application: ELISA

   Rat IL-4 Quantikine ELISA Kit (Catalog # R4000)
   Sample: Rat bronchoalveolar and bone marrow lavage fluids
   Application: ELISA

   Rat IL-10 Quantikine ELISA Kit (Catalog # R1000)
   Sample: Rat bronchoalveolar and bone marrow lavage fluids
   Application: ELISA

6. Piconi, S. *et al.* (2007) Effects of specific immunotherapy on the B7 family of costimulatory molecules in allergic inflammation. J. Immunol. **178**:1931.

   Human CTLA-4 Fluorescein Monoclonal Antibody (Catalog # FAB325F)
   Sample: Human peripheral blood mononuclear cells
   Application: Flow cytometry

   Human CD28 Monoclonal Antibody (Catalog # MAB342)
   Sample: Human peripheral blood mononuclear cells
   Application: Functional assay - T cell stimulation

7. Garcia, G. *et al.* Chemokine receptor expression on allergen-specific T cells in asthma and allergic bronchopulmonary aspergillosis. Allergy **62**:170.

   Human CD4 Phycoerythrin Monoclonal Antibody (Catalog # FAB3791P)
   Sample: Human resting and allergen-specific $CD4^+$ T cells
   Application: Flow cytometry

   Human CCR8 Fluorescein Monoclonal Antibody (Catalog # FAB1429F)
   Sample: Human resting and allergen-specific $CD4^+$ T cells
   Application: Flow cytometry

   Human CD3ε Allophycocyanin Monoclonal Antibody (Catalog # FAB100A)
   Sample: Human resting and allergen-specific $CD4^+$ T cells
   Application: Flow cytometry

   Human CCR4 Fluorescein Monoclonal Antibody (Catalog # FAB1567F)
   Sample: Human resting and allergen-specific $CD4^+$ T cells
   Application: Flow cytometry

   Human CCR3 Fluorescein Monoclonal Antibody (Catalog # FAB155F)
   Sample: Human resting and allergen-specific $CD4^+$ T cells
   Application: Flow cytometry

   Human CXCR3 Fluorescein Monoclonal Antibody (Catalog # FAB160F)
   Sample: Human resting and allergen-specific $CD4^+$ T cells
   Application: Flow cytometry

   Human CXCR4 Fluorescein Monoclonal Antibody (Catalog # FAB170F)
   Sample: Human resting and allergen-specific $CD4^+$ T cells
   Application: Flow cytometry

8. Razafindratsita, A. *et al.* (2007) Improvement of sublingual immunotherapy efficacy with a mucoadhesive allergen formulation. J. Allergy Clin. Immunol. **120**:278.

   Mouse IL-5 ELISpot Development Module (Catalog # SEL405)
   Sample: Mouse splenocytes
   Application: ELISpot

   Mouse IFN-γ ELISpot Development Module (Catalog # SEL485)
   Sample: Mouse splenocytes
   Application: ELISpot

   Mouse IL-10 Quantikine ELISA Kit (Catalog # M1000)
   Sample: Mouse splenocyte supernates
   Application: ELISA

9. Daines, M.O. *et al.* (2007) Allergen-dependent solubilization of IL-13 receptor α2 reveals a novel mechanism to regulate allergy. J. Allergy Clin. Immunol. **119**:375.

   Human IL-13 sRα 2 DuoSet ELISA (Catalog # DY614)
   Sample: Human bronchoalveolar lavage fluid
   Application: ELISA

10. Goleva, E. *et al.* (2007) Airway remodeling and lack of bronchodilator response in steroid-resistant asthma. J. Allergy Clin. Immunol. **120**:1065.

    Human MMP-9 Quantikine ELISA Kit (Catalog # DMP900)
    Sample: Human bronchoalveolar lavage fluid
    Application: ELISA

    Human TIMP-1 Quantikine ELISA Kit (Catalog # DTM100)
    Sample: Human bronchoalveolar lavage fluid
    Application: ELISA

    Human VEGF Quantikine ELISA Kit (Catalog # DVE00)
    Sample: Human bronchoalveolar lavage fluid
    Application: ELISA

11. Fawaz, L.M. *et al.* (2007) Expression of IL-9 receptor α chain on human germinal center B cells modulates IgE secretion. J. Allergy Clin. Immunol. **120**:1208

    Human IL-9 R Monoclonal Antibody (Catalog # MAB290)
    Sample: Human tonsil-derived B cells
    Application: Immunohistochemistry

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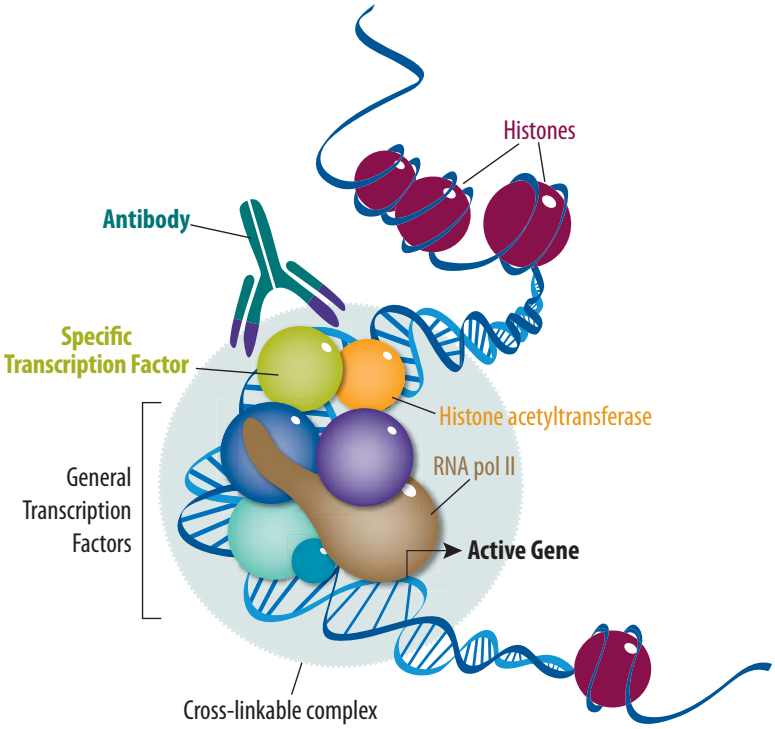
FoxP3	ECP3240	Smad4	ECP2097
GATA-4	ECP2606	SOX2	ECP2018
GATA-6	ECP1700	STAT3	ECP1799
GLI-2	ECP3526	STAT5a/b	ECP2168
KLF4	ECP3640, ECP3158 (M)	M = Mouse	



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