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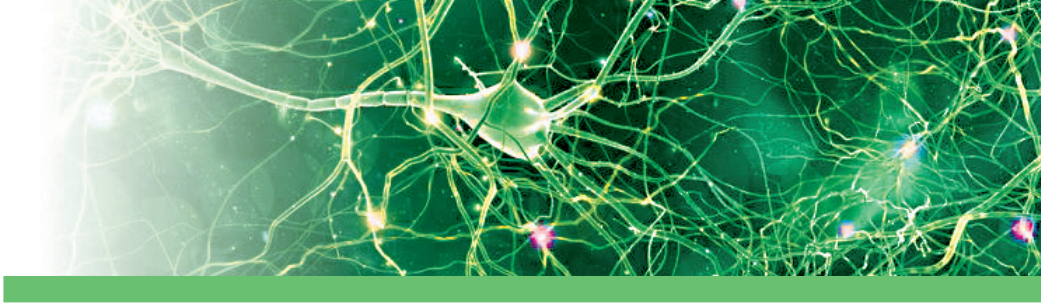
LIFE SCIENCES
insights



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Interleukin-33

NEW Function of a Key Cytokine in Brain Development & Neurological Diseases

IL-33, a member of the IL-1 cytokine family, is constitutively expressed in fibroblasts, endothelial and epithelial cells exposed to the environment. IL-33 is a nuclear-associated cytokine that is normally released by damaged or necrotic cells acting as an "alarmin", an immediate indicator of tissue stress.

IL-33 signals through ST2 coupled with the co-receptor IL-1 receptor accessory protein (IL-1RAcP). IL-33 is a potent inducer of type 2 immune responses in the contexts of parasite infections and allergic asthma. New studies have also extended the biology of IL-33 with other functions: i) inducing brown and beige adipocyte thermogenesis and to promote insulin secretion by pancreatic islets; ii) facilitating Treg proliferation to suppress autoimmunity and to potentiate neurological recovery; and iii) exerting multiple roles in the brain.

IL-33 is abundantly expressed in specific regions of brain and spinal cord, mediates the interaction between immune, endothelial and CNS (central nervous system) resident cells and plays a key role in the development and homeostasis of the CNS. Astrocytes are the primary source of local IL-33 that stimulates synapse elimination by microglia during early CNS development (see FIGURE 1). Deletion of IL-33 in astrocytes leads to abnormal synaptic connections. IL-33 is involved in the neuro-inflammation of many neurological diseases such as Alzheimer's disease (AD) and multiple sclerosis (MS).

Different studies suggest that IL-33 is involved in the myelination process during the CNS development and also likely the repair phase in demyelinating diseases such as MS and that IL-33 plays a critical role in the maintenance and repair of aging and stressed neurons during AD.

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SELECTED ARTICLES

Astrocyte-derived interleukin-33 promotes microglial synapse engulfment and neural circuit development: I.D. Vainchtein, et al.; Science **359,** 1269 (2018) • Expression and Function of IL-33/ST2 Axis in the Central Nervous System Under Normal and Diseased Conditions: K. F Fairlie-Clarke, et al.; Front. Immunol. **9,** 2596 (2018) • IL33: Roles in Allergic Inflammation and Therapeutic Perspectives: B.C.L. Chan, et al.; Front. Immunol. **10,** 364 (2019)

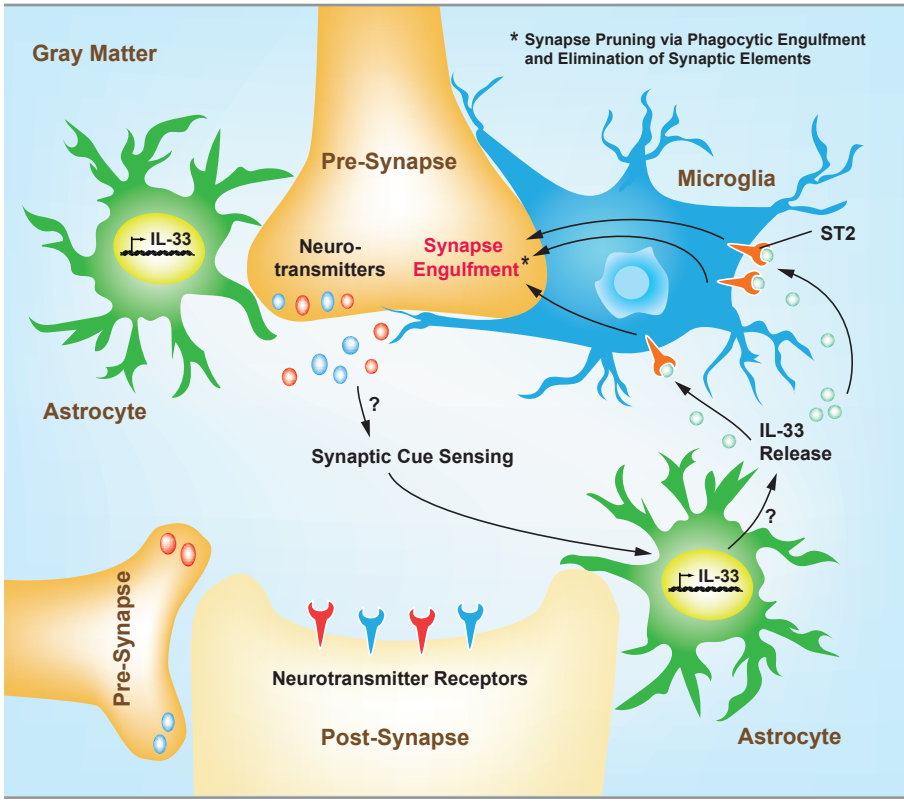

FIGURE 1: Astrocyte-derived IL-33 stimulates synapse elimination by microglia during CNS development.

Most Comprehensive & Unique IL-33 Reagents for Type 2 Immune Response Research

UNIQUE

IL-33 Blocking Antibody

The IL-33 (mouse), mAb (rec.) (blocking) (Bondy-1-1) (Prod. No. AG-27B-0013) is a recombinant antibody developed and produced in-house at AdipoGen Life Sciences. It is produced without the use of animals and purified from HEK 293 cell culture supernatant. This unique antibody has functional activities and inhibits the binding of mouse IL-33 to ST2/IL-1RAcP.

anti-IL-33 (mouse), mAb (rec.) (blocking) (Bondy-1-1)

AG-27B-0013		100 µg
AG-27B-0013PF	Preservative Free	100 µg | 500 µg | 1 mg

Isotype Mouse IgG2b
Application ELISA, FUNC (Blocking)

Functional Application
Inhibits the binding of mouse IL-33 to ST2/IL-1RAcP.

LIT: Regulation of de novo adipocyte differentiation through crosstalk between adipocytes and pre-adipocytes: T.D. Challa, et al.; Diabetes **64,** 4075 (2015) • Male-specific IL-33 expression regulates sex-dimorphic EAE susceptibility: A.E. Russi, et al.; PNAS **(epub ahead of print)** (2018)

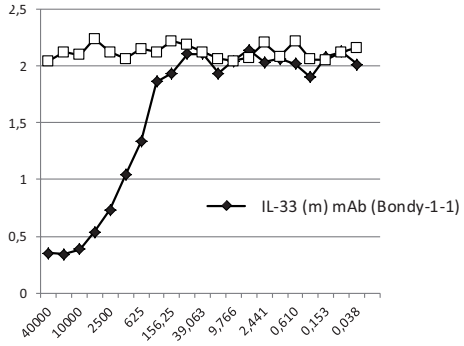

FIGURE: Binding of IL-33 (mouse) to ST2/IL-1RAcP is inhibited by Bondy-1-1 (Prod. No. AG-27B-0013). IL-33 (mouse) was coated on an ELISA plate at 1µg/ml. Bondy-1-1 or an unrelated mAb (recombinant) (Control) were added (starting at 40µg/ml with a twofold serial dilution) together with 100µl of supernatant of cells containing ST2 (human):Fc/IL-1RAcP (human):Fc. After incubation for 1 h at RT, the binding was detected using an anti-Fc human antibody (HRP).

UNIQUE

Highly Active Human IL-33 Proteins

IL-33 (oxidation resistant) (human) (rec.) (untagged) (Prod. No. AG-40B-0160) and IL-33 (oxidation resistant) (human) (rec.) (His) (Prod. No. AG-40B-0167) are both specifically designed proteins. The biological activity of IL-33 at its receptor ST2 is rapidly terminated in the extracellular environment by its oxidation (formation of two disulfide bridges), resulting in an extensive conformational change that disrupts the ST2 binding site. Mutations at amino acids C208S/C232S protect IL-33 from oxidation and increase its activity.

LIT: Oxidation of the alarmin IL-33 regulates ST2-dependent inflammation: E.S. Cohen, et al.; Nat. Commun. **6,** ID8327 (2015)

IL-33 (oxidation resistant) (human) (rec.)

AG-40B-0160	Untagged	10 µg | 100 µg
AG-40B-0167	His-tagged	10 µg | 100 µg

LIT: Oxidation of the alarmin IL-33 regulates ST2-dependent inflammation: E.S. Cohen, et al.; Nat. Commun. **6,** ID8327 (2015)

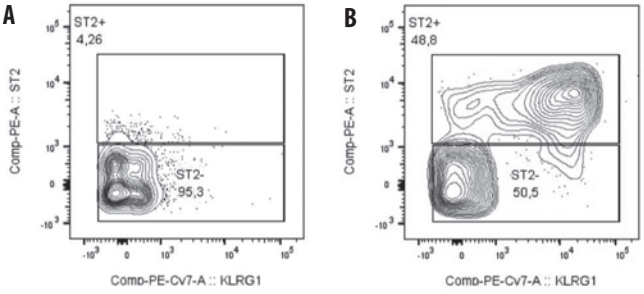

FIGURE: Activation *in vivo* of Innate Lymphoid Cells 2 (ILC2) by IL-33 (oxidation resistant) (human) (rec.) (untagged) (AG-40B-0160). Method: C57BL/6 mice were injected daily for 3 days with PBS (Figure A) or IL-33 (oxidation resistant) (human) (rec.) (untagged) (AG-40B-0160) (at 0.4µg per mouse) (Figure B). At day 4, cells from bone marrows were stained and analyzed by flow cytometry. Levels of ST2 and KLRG1 on Innate Lymphoid Cells (gated as lineage negative, CD127 positive cells) are shown. *Picture courtesy of Dr G.Verdeil / Dr S. Trabanelli (Camilla Jandus Group, Department of Fundamental Oncology, University ofLausanne).*

AdipoGen® LIFE SCIENCES

APPLICATIONS: FACS: Flow Cytometry; **FUNC:** Functional Application; **ICC:** Immunocytochemistry; **IHC:** Immunohistochemistry **IP:** Immunoprecipitation; **WB:** Western blot

FORMULATION: PF = Preservative free
SPECIES: Hu = Human; **Ms** = Mouse; **Rt** = Rat; **Rb** = Rabbit; **Prm** = Primate

UNIQUE

HpARI – Suppressor of Type 2 (Allergic) Immune Response

AdipoGen Life Sciences' HpARI (Alarmin Release Inhibitor) (rec.) (His) (Prod. No. AG-40B-0178) is a recombinant produced protein. HpARI is a protein normally secreted by the mouse parasite *Heligmosomoides polygyrus*. The mature protein HpARI, containing three predicted Complement Control Protein (CCP)-like modules (also known as Short Consensus Repeats (SCRs) or sushi-domains), suppresses type 2 (allergic) immune responses through interference in the interleukin-33 (IL-33) pathway. During cell damage, HpARI gains access to the nucleus of necrotic cells, where it binds directly to IL-33 and nuclear DNA, preventing secretion and binding of IL-33 to its receptor. HpARI is a new type of reagent to prevent IL-33-mediated pathology.

HpARI (Alarmin Release Inhibitor) (rec.) (His)

AG-40B-0178 — 50 µg | 3 x 50 µg

Specific for human and mouse.

During cell damage, HpARI gains access to the nucleus of necrotic cells, where it binds directly to IL-33 and nuclear DNA, preventing secretion and binding of IL-33 to its receptor.

LIT: M. Osbourne, et al.; Immunity **47,** 739 (2017)

Source/Host HEK 293 cells
Sequence Heligmosomoides polygyrus protein HpARI (aa 17-251) is fused at the C-terminus to a His-tag.
Specificity Binds to human and mouse IL-33.
Purity ≥90% (SDS-PAGE)

POTENT

POTENT ST2-specific Antibody for Flow Cytometry

AdipoGen Life Sciences' anti-ST2 (human), pAb (Prod. No. AG-25A-0058) is a polyclonal antibody that recognizes solube human ST2 in Western blot and Flow Cytometry. Soluble ST2 plays a role in protecting ILC2 from IL-33 stimulation and thereby maintaining them in a naïve state and it might be important for the regulation of several disease. This antibody is available unlabeled and as labeled versions with ATTO 448 (Prod. No. AG-25A-0058YTD) and ATTO 647N (Prod. No. AG-25A-0058YTS).

anti-ST2 (human), pAb

AG-25A-0058		100 µg
AG-25A-0058YTD	ATTO 488	100 tests
AG-25A-0058YTS	ATTO 647N	100 tests

Source/Host Rabbit
Immunogen Recombinant human soluble ST2.
Application ELISA, FC, WB
Specificity Recognizes soluble human ST2. Detects a band of ~50kDa by Western blot and the endogenous ST2 by Flow Cytometry.

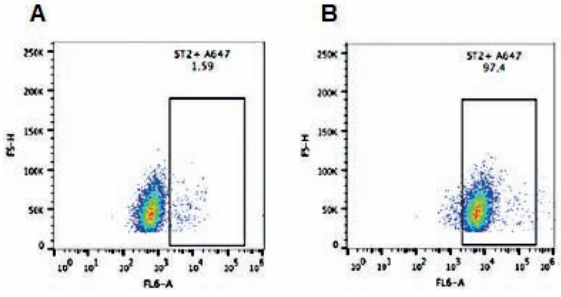

FIGURE: Detection of endogenous human ST2 with anti-ST2 (human), pAb (AG-25A-0058).
METHOD: THP1 cells were stained with anti-ST2 (human), pAb (1:100 in PBS + 2% FCS) (Figure B) or with the secondary antibody alone (Figure A) for 1h at 4°C.

Other IL-33 Related Antibodies & Assays

PRODUCT NAME	PID	PRODUCT DESCRIPTION
ST2 (human):Fc (human) (rec.)	AG-40A-0059	Interacts with human IL-33.
IL-33R [ST2] (human):Fc (human) (rec.)	CHI-HF-21033R	Measured by its ability to bind recombinant human IL-33 in a functional ELISA.
IL-33R [ST2] (mouse):Fc (mouse) (rec.)	CHI-MF-11033R	Measured by its ability to bind recombinant mouse IL-33 in a functional ELISA.
anti-ST2 (human), mAb (ST33868)	AG-20A-0044	Recognizes human ST2 in Immunohistochemistry and Western blot.

Other IL-33-related Proteins, Antibodies & Assays

PRODUCT NAME	PID	PRODUCT DESCRIPTION
IL-33 (human) (rec.) (untagged)	AG-40B-0038	Activates human and mouse ST2-dependent NF-κB pathway.
IL-33 (human) (rec.) (His)	AG-40A-0042	Activates human ST2-dependent NF-κB pathway.
IL-33 (mouse) (rec.) (untagged)	AG-40B-0041	Activates mouse and human ST2-dependent NF-κB pathway.
IL-33 (mouse) (rec.) (His)	AG-40A-0053	Activates mouse and human ST2-dependent NF-κB pathway.
anti-IL-33, mAb (IL33026B)	AG-20A-0043	Recognizes human and mouse IL-33 in Immunoprecipitation and Western blot.
anti-IL-33 (human), mAb (IL33305B)	AG-20A-0041	Recognizes human IL-33 in Functional, Immunohistochemistry, Immunoprecipitation and Western blot.
anti-IL-33 (human), pAb	AG-25A-0045	Recognizes recombinant human IL-33 in Immunohistochemistry and Western blot.
anti-IL-33 (mouse), pAb	AG-25A-0047	Recognizes mouse IL-33 in Western blot.
anti-IL-33 (mouse), mAb (rec.) (Carly-1-4)	AG-27B-0012	Recognizes mouse IL-33 in Western blot.
IL-33 (human) ELISA Kit	AG-45A-0033Y	Detects human IL-33. Does not cross-react with mouse IL-33 or human ST2.

IL-33 and Adipose Tissue Homeostasis

Lean adipose tissue contains adipocytes, regulatory immune cells and adipose stroma that contribute to fat tissue homeostasis. Adipocytes of lean tissue secrete adipokines (e.g. adiponectin, an anti-inflammatory protein), which play important roles in the regulation of systemic metabolism (immunometabolism) and have a profound impact on immune cell behavior. These immune cells maintain homeostasis, preserving insulin sensitivity and glucose tolerance and keeping adipose tissue macrophages (ATMs) in an anti-inflammatory M2-like state [1].

During high-fat diet and obesity, fat cells increase (hypertrophy) producing less adiponectin and more pro-inflammatory molecules such as leptin, IL-6 and monocyte chemo-attractant protein-1 (MCP-1). Inflammatory immune cells detect adipose stress, accumulate and secrete IFN-γ, driving pro-inflammatory M1 macrophage differentiation leading to a chronic inflammatory state.

IL-33 is of particular importance for adipose homeostasis. Although upon infection and allergy, IL-33 is classified as a pro-inflammatory mediator, under non-inflammatory conditions IL-33 sustains Tregs, eosinophils as well as ILC2 to keep an anti-inflammatory state in adipose tissue (see FIGURE 2). IL-33 is also involved in the formation of brown adipocytes from adipocyte precursors by a mechanism involving IL-13 and the endogenous opioid Met-Enkephalin secreted by activating ILC2s [2]. A direct negative role of IL-33 on adipocyte differentiation has been reported recently [3].

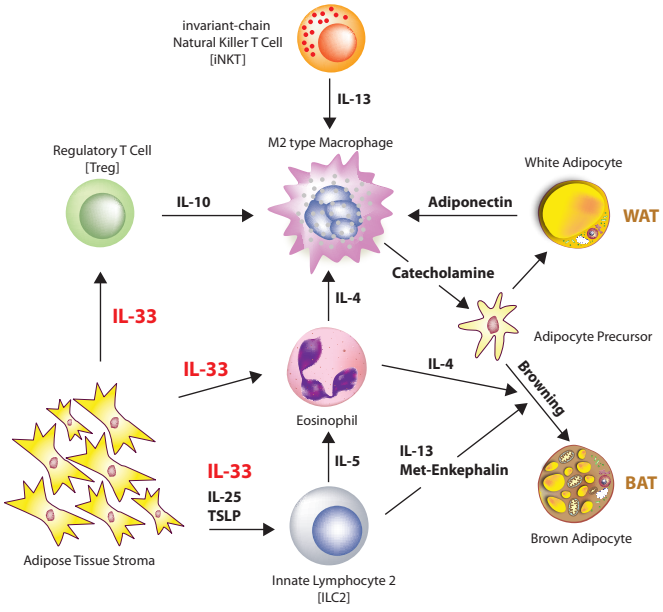

FIGURE 2: Control of adipose tissue homeostasis.

LIT: [1] The "Big Bang" in obese fat: Events initiating obesity-induced adipose tissue inflammation: F.M. Wensveen, et al.; Eur. J. Immunol. **45,** 2446 (2015) • **[2]** Activated type 2 innate lymphoid cells regulate beige fat biogenesis: M.W. Lee, et al.; Cell **160,** 74 (2015) • **[3]** Regulation of de novo adipocyte differentiation through crosstalk between adipocytes and pre-adipocytes: T.D. Challa, et al.; Diabetes **64,** 4075 (2015)

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