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Original Article

Biology of Interleukin 33 (IL-33)

Talat Abdullah Al-bukhari.
Department of haematology & immunology, Faculty of Medicine, Umm Al-Qura University, Makkah, Saudi Arabia.

Correspondence :
Dr. Talat Abdullah Al-bukhari
Department of haematology & immunology, Faculty of Medicine, Umm Al-Qura University, Makkah, Saudi Arabia, P.O. Box: 7607
Fax: 00966125270000-4161
E-mail: tabukhari@uqu.edu.sa

العلم الحيوي لانترلوكين 33

د. طلعت بن عبد الله البخاري
قسم الدم والمناعة – كلية الطب –جامعة ام القرى– مكة المكرمة – المملكة العربية السعودية.

الملخص

انترلوكين 33(IL-33) هو عضـو جديد من عائلة محفز الخلايا انترلوكين1 (IL-1) والذي يبدي وظيفة حيوية من خلال مستقبل الخلايا الخاص به وهو ST2 .

الفكرة البدائية كانت توضــح أن انترلوكين 33 يبدي وظيفة حيوية في خلايا تي المســاعدة 2 (Th2) الحاملة لـــــ CD4 والمرتبط إيجابياً مع ST2 الذي على سطحها من خلال انتاجَ IL-5 وَ IL-13 .

من المثير للاهتمام أن الدراسات الأخيرة تقترح أن انترلوكين 33 أيضاً قد يكون مسؤولاً عن استجابة خلايا تي المساعدة 1 (Th1) في المناعة الطبيعية والحالات المرضــية . على أي حال , ســواءاً انترلوكين 33 قادراً على تحفيز خلايا تي المساعدة 1 أو لا , والذي لا يزال مجهولاً حالياً .

ABSTRACT

Interleukin-33 (IL-33) is a new member of the IL-1 cytokine family which exerts biological function via its cellular receptor ST2. The initial thought was that IL-33 exerts a vital function in ST2-positive type 2 $CD4^+$ T helper (Th2) cells response through the induction of IL-5 and IL-13. Interestingly, recent studies have suggested that IL-33 may be also involved in Th1 cell responses in immunity and disease. However, whether IL-33 can polarise Th1 cells or not is currently unknown.

Keywords: IL-33, Th1/Th2, St2 receptor

INTRODUCTION

IL-33 was discovered as a new member of the IL-1 family in 2005 (1).
The members of the IL-1 cytokine family including IL-1α, IL-1β and ……. IL-18, possess similar homological structure and nucleotide sequences and play a critical role in immunity, infection and inflammation (2-3). IL-33 is produced as a pro-protein about 32KDa which can be further matured by undefined enzymes to produce 18KDa mature protein (1).

Pro-IL-33 contains a DNA-binding domain which allows the protein to interact with chromosomal DNA in the nucleus may play a regulatory role in gene function (1). There is 55% identical homology at the amino acid level between murine and human *IL-33* (1). The mRNA level of IL-33 can widely detected in tissues such as lung, brain, stomach, spin cord and skin (1). However, the expression of IL-33 mRNA is only observed in a few cell types such as epithelial cells, smooth muscle cells (SMC), activated macrophages and dendritic cells (DC) (1).

METHODS

RECEPTOR FOR IL-33

IL-33 is thought to perform its biological function through a receptor complex consisting of ST2 and IL-1 receptor accessory protein (IL-1RAP) (1, 4). Even though IL-1RAP is necessary for signalling of IL-33, IL-33 mainly signals via ST2 (1). ST2 is a member of IL-1 receptor (IL-1R) family and is mainly on innate immune cells such as mast cells and basophils (5), eosinophils (6) and DC (7). It also preferentially induced and expressed on Th2 cells, but not Th1 cells (8-9). IL-33 also is expressed by structural cells, such as epithelial cells, endothelial cells and fibroblasts which play a major role in the immune system (10).

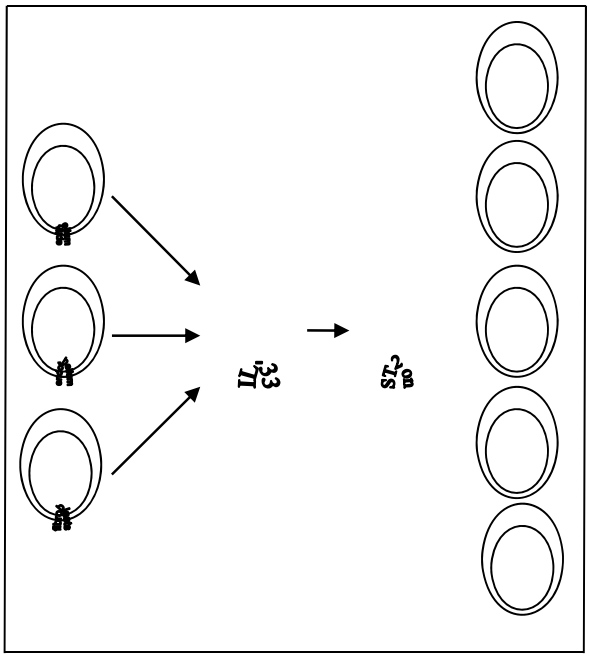

Figure1: IL-33 production and receptors

FUNCTION OF IL-33

The interaction between IL-33 and its receptors initiates the recruitment of myeloid differentiation primary-response protein 88 (MYD88) complexes to activate the transcription factor nuclear factor- kappa B (NF-κB) and mitogen-activated protein kinases (MAPKs), leading to cytokine production and cellular activation (1). It has been reported that IL-33 can drive production of Th2-secreted cytokines such as IL-5 and IL-13 but not IL-4 by either polarised Th2 cells or naïve T cells independent of IL-4 (1, 11). Furthermore, increased mRNA levels of IL-5 and IL-13 can be observed in spleen, thymus and lung by stimulation with IL-33 *in*

vivo (1). Schmitz and colleagues also reported that IL-33 can induce high level of serum IgE production, splenomegaly and eosinophilia in mice. These findings indicate that IL-33 may be a key factor for Th2 response in immunity and disease.

In addition, IL-33 can stimulate Th2-associated cytokines and protect against parasite infection and arthrosclerosis (2, 12). IL-33 also play a critical role in allergic disease and asthma due to its important function on Th2 cells, mast cells, basophils and eosinphils in allergic responses (11, 13-17).

However, several studies have revealed that IL-33 might also be involved in the Th1-mediated response (18-20). It has been reported that IL-33 can induce IFN-γ from invariant natural killer T (iNKT) cells as well as natural killer (NK) cells in the presence of IL-12 (19). It can also promote the production of pro-inflammatory cytokines such as IL-17, TNF-α and IFN-γ in mice of collagen-induced arthritis (CIA), a model for human rheumatoid arthritis (21). Thus, IL-33 can mediate Th1 cells response separately from its function in Th2 cells responses. It is also reported that IL-33 can activates the $CD8^+$ T cells and NK cells that could directly kill tumor cells. These observation show that IL-33 function like as IL-18 that can activate both Th1 or Th2 base on condition and act as a alarmins for immune system(22).

'Alarmins' are a group of endogenous proteins or molecules that are released from cells during cellular demise to alert the host innate immune system. It also activates the indirect anti-tumor immune cells such as dendritic cell (DC)(23).

Cell activation	Cytokine and Ab production	Disease
Th2	IL-5 and IL-13	Protect against parasite infection and arthrosclerosis
Th2 cells, mast cells, basophils and eosinphils	high level of serum IgE	allergic responses
$CD8^+$ T cells and NK cells	------	kill tumor cells
NK and iNKT cells in the presence of IL-12	IFN-γ	------
------	IL-17, TNF-α and IFN-γ in mice of CIA	------

Table 1: Function of IL-33

CONCLUSIONS

Cytokines play a critical role in the control of the innate and adaptive immune responses. IL-33, the most recently discovered member of the IL-1 superfamily including IL-1 and IL-18 and have been linked to several human pathologies. Il-33 strongly bind to ST2 receptor that is mainly expressed on stromal cell and Th2 cells. IL-33 has shed new light on the intricacies of immune system regulation. These novel cytokines have pleiotrophic actions ranging from antiviral immunity to the regulation of Th2 immune responses. For example, the discovery of IL-33 has significantly improved our understanding of the factors regulating the polarization of the T helper cell responses and IL-33 appears to be an important regulator of Th2 responses.

On the other hand, IL-33 considered to be critical for mounting an efficient antiviral response, which are yet to be fully characterized, are emerging as important components of the inflammatory response in allergy and autoimmunity. IL-33 and other cytokine/receptor combinations may, therefore, serve as novel targets for the

treatment and control of allergy, autoimmune diseases, and some cancers.

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