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THE ROLE OF IL-33 IN THE INFLAMMATION PROCESS OF ASTHMA AND ATHEROSCLEROSIS

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Abstract
Interleukin-33 (IL-33) is a newly found cytokine of the interleukin-1 (IL-1) family. It's mainly expressed by epithelial and endothelial cells. This expression is upregulated by pro-inflammatory stimulation, thus has an important role in inflammatory responses, such as hypersensitive diseases (asthma), autoimmune diseases (rheumatoid arthritis), cardiovascular diseases (heart failure) and neurodegenerative diseases (Alzheimer). Several studies explored the complicated mechanism of IL-33 action in asthma and atherosclerosis, as this IL is significantly increased in these pathologies, and suggested its potential use in the therapeutic procedures.

INTRODUCTION

Atherogenesis

Aterogenesis is a degenerative disease as a consequence of inflammation in the vessel walls. It's an increasing cause of mortality and morbidity in the general population. The consequences of atherosclerosis and deaths from atherosclerotic cardiovascular disease in the closest future will replace, in the Third World, the frequency of deaths caused by infections (1).

There are different hypothesis which try to explain the atherogenesis development:

Lipid hypothesis - proposed the first time by Anitschkow in 1913. The development of atherosclerosis is the result of the gradual accumulation of lipid in the arterial wall, which cause the atheroma characteristics .

Thrombogenic hypothesis - the atherosclerotic lesions grow with the gradual incorporation of thrombus on arterial wall. This theory is difficult to prove because plaque infiltration by immature blood vessels is common in advanced lesions, consequent hemmorhage and thrombosis also occur frequently and thrombus can appear directly as a result of atherosclerosis.

The triggering event in these two hypotheses can be considered the endothelial dysfunction. In the lipid hypothesis because a defective endothelial cell barrier make simpler the lipid accumulation into the arterial intima layer, then the beginning of plaque development. In the thrombogenic theory the dysfunctional endothelium can promote the local platelet aggregation which will be enclosed into the arterial wall. (2)

Injury hypothesis - This hypothesis was revised few times leading to the following version, where the endothelial dysfunction from any cause, and not necessary mechanical injury, is very important in the atherosclerosis development. These agents which cause the injury are what today we consider atherosclerosis risk factors: hypertension, hyperlipidemia, cigarette smoking (3,4).

Inflammation theory - Not only the endothelium play a central role in the phatogenesis of atherosclerosis but also the inflammation (2).

The importance of endothelial cells was discovered by Ross in the '70. Ross removing the endothelial cells and using a lipid-rich diet, showed that atherosclerosis was developed. Today,the endothelial cells are considered as a tissue or organ because of their autocrine, paracrine and endocrine activity. Endothelium controls many processes: vascular tone, stimulates the smooth muscle cells (SMC), immunity response, monocyte's adhesion, platelet aggregation, nitric oxide (NO) production.

Also the NO plays the important functions: anti –piastrinic activity, reduces the inflammatory cell recruitment into the intima layer preventing the gene expression involved in that process, as gene which encode for intercellular adhesion molecules-1 (ICAM-1) or vascular cell adhesion molecules-1 (VCAM-1), stimulates the SMC (5,6,7) .

In diabetic, hypercholesterolemic and hypertension states increased production of free radicals is observed . These reactive oxygen species interact with NO, developing the peroxynitrite (ONOO-) and subsequently powerfull free radicals, such as hydroxyl (-OH) and nitrogen dioxide (NO2). The peroxynitrite can interact with lipoproteins such as LDL (producing lipoperoxides) which has different negative effects: cytotoxicity for endothelial cells, promotion of the adhesion of vascular inflammatory cells .Ox-LDL are internalized by macrophages with consequent inflammation response and recruitment of lymphocytes in the inflammed area. So there is the production of foam cells, which are the signal for SMCs and fibroblasts to realease connective tissue matrix. All these steps lead to plaque development (8,9,10). With the growth of plaques and their damaging, the consequent endothelium damaging and thrombus development occurs.

Macrophages recognize the Ox-LDL by many types of scavenger receptors which are able to bind different kind of ligands. Their expression is mediated by inflammation mediators, such as cytokines (11,12) .

The inflammation response in the atherosclerotic area, initiates and maintains activation of overlying endothelial cells. The activated cells express different selectines, adhesion molecules (AM) and chemokines which are proinflammatory cytokines responsible for migration, chemoattraction and activation of leukocytes. (9) The selectine molecules mediated the inflammatory cell recruitment on the atherosclerotic area.

In the contrary to LDL, the HDL particles have a protective effect. They are involved in the evolution of chylomicrons, VLDL, and they have the ability to block the endothelial cell expression of adhesion molecules and are responsible for reverse cholesterol transport from the periferal tissues to the liver or steroidogenic tissues as adrenal glands or gonads (13,14).

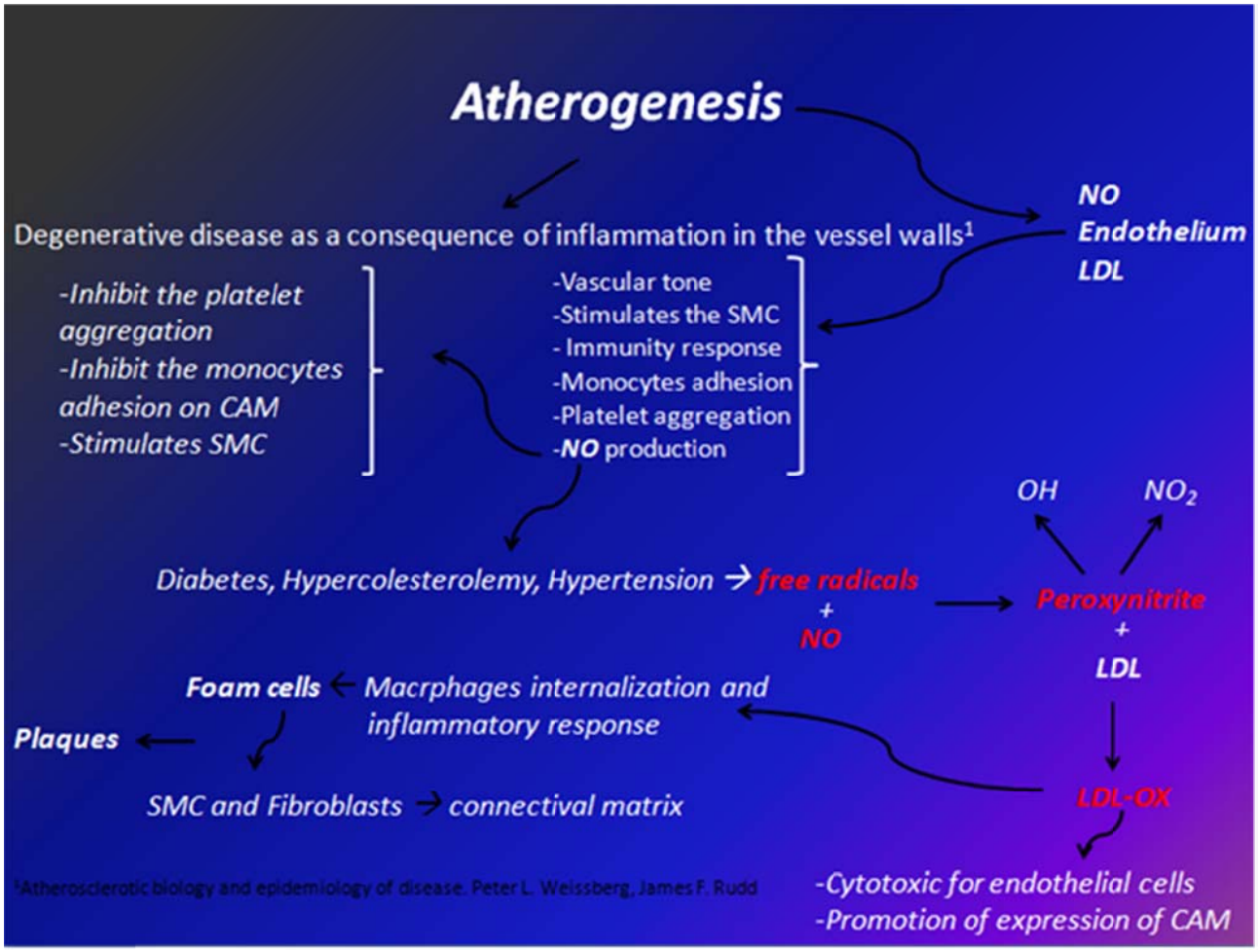

Figure 1. Scheme of atherosclerosis development.

The process of plaque development and consequently rupture is an inflammatory condition. Different studies have demonstrated correlation between the levels of C-reactive protein (CRP) and risk of plaque rupture (15,16,17,18) . Other inflammatory markers as soluble ICAM-1 (19), VCAM-1 (20,21), P-selectin (22), interleukin-6 have been shown the primary drivers to CRP production (23) .

The Lp-PLA2 , an enzyme that circulate in the blood can bind the LDL particles. It was also found

on vessel walls where the oxidation process took place. The researchers analyzed data of 32 prospective studies, showing in altogether 79.036 patients that the high concentration of Lp-PLA2

was associated with an increased risk for coronary artery disease (the risk was observed to be the same as for hypertension and hypercholesterolemia) (24). The selective inhibition of Lp-PLA2 has been proposed to reduce the progression of core necrosis and the clinical development of atherosclerosis (25).

Asthma

Asthma is a chronic inflammatory disease of the airways that involves a very complex cell interaction, mediators, cytokines and chemokines and is associated with variable airflow limitation, superimposed bronchospasm and increased airway responsiveness (NIH guidelines 1997). Asthma

leads to wheezing, breathlessness and cough (26,27). Asthma is episodic in nature and usually reversible, either spontaneously or with treatment. However, chronic inflammation, associated with persistent symptoms, may contribute to airway remodeling that may not be completely reversible. Asthma symptoms are often "triggered" by:

environmental stimuli (smoke, perfumes, dust mites, animals, fungi/molds, cold air) and aggravating conditions (viral upper respiratory infections or URIs, rhinitis, sinusitis, gastroesophageal reflux, stress, exercise). Such triggers may be more important for some asthma phenotypes than others (28,29).

National Heart, Lung, and Blood Institute (NHLBI) Guidelines for the Diagnosis and Management of Asthma, published in 2007 (28) estimate that in U.S. there are 6 millions asthmatics. In 2006 the prevalence of asthma in children between 0-17 years of age was 7.5% in males and 5.5% in females (30) but, considering other age groups, asthma have higher prevalence in females (31). For unknown reasons, asthma has dramatically increased in prevalence over the last several decades along with allergies. Although about one half of people with asthma also have allergies, but not all people with allergies have asthma and the association between asthma and allergy, is not clear.

Multiple reports identified differences among some demographic groups by age, sex, race/ethnicity (32,33). These reports indicate that population-based asthma prevalence rates, emergency department visit rates, and hospitalization rates were higher for black race patients than whites, higher for females than males, higher for children than adults, and higher for males aged 0-17 years age than for females with the same age (34,33).

Asthma is a complex disease caused by the interaction of host and environmental factors at some critical period during the development of the immune system. All asthmatic children have a specific contributing factors, so even the therapy may be different (35,36). The most important host factors are genetic factors. If the child's mother has asthma, the child has higher probability to have asthma than if the child's father has asthma. If both parents have asthma, their child has a 50% probability to have asthma. Different genes have been identified that may be important in the asthma, including (ADAM)33 on chromosome 20p13, which regulates, metalloproteinase, an enzyme which is involved in the airway smooth muscle cells (37).

A subgroup of lymphocytes, T helper (Th) cells type 2 (Th2) are the major allergy-asthma controlling cells. Th2 cells are responsible for the releasing of immune factors - interleukins, involved in the inflammatory response. Some interleukins (IL-4, IL-13) are responsible for the first-phase of asthma attack by producing IgE, which binding to mast cells allow to release leukotrienes that are responsible for the airway spasms and increased mucus production. Other interleukins (IL-5) are responsible for the late-phase of asthma attack, where lead the eosinophil accumulation and release other immune factors. The asthma medications have this system as a target, but recently also the T killer cells have been connected with the asthma response and it may be a reason for why some patients doesn’t respond to the medications (28) .

In contrast to Th2 cells which are the asthma and allergy T cells, Th1 cells are involved in the infection responses. With the increasing of Th1 cell response the Th2 cell response decreases. It is known that the Th1 response increase with smaller use of antibiotics, increased exposure to other children, and exposure to certain infections, such as the common cold with a subsequent decrease in asthma frequency and a decreased Th2 response. This has developed the "hygiene hypothesis" in which early exposure to allergens and infection may prevent allergic and asthmatic responses (38,28).

Inflammation

Inflammation is an important process involved in atherosclerosis as in asthma. It is a non-specific response which the organism activate to tissue damage by exogenous stimuli (physical: burns, trauma; chemical: toxic substances; biological: microorganisms, parasites) or endogenous stimuli (metabolic and/or immune disorders). It has a defensive purpouse, activates the immune system in the site where there is the biological intrusion and start the tissue reconstruction to repair the damage. Inflammatory pathways and anflammatory effects are presented on Figures 2 and 3.

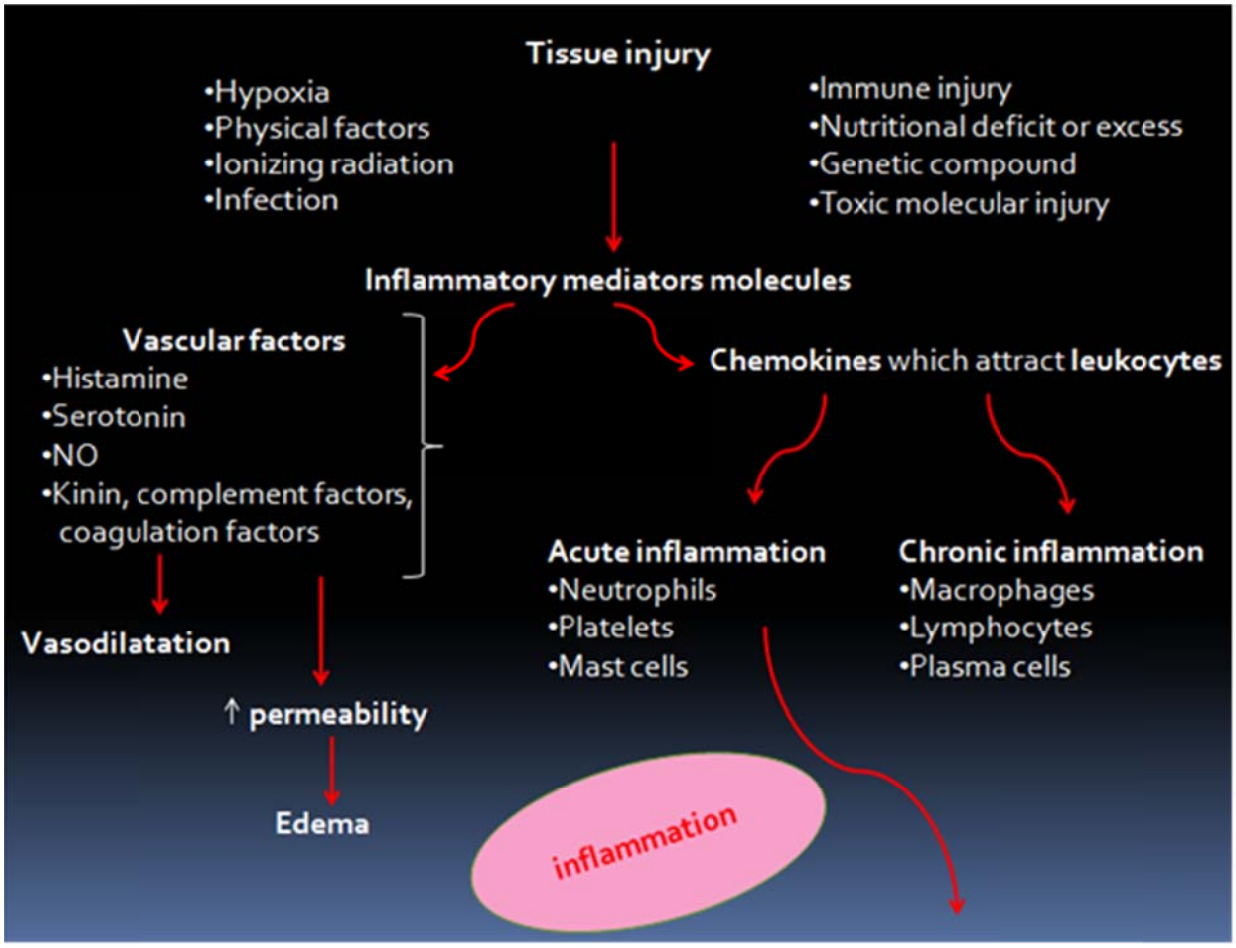

Figure 2. Inflammatory pathways

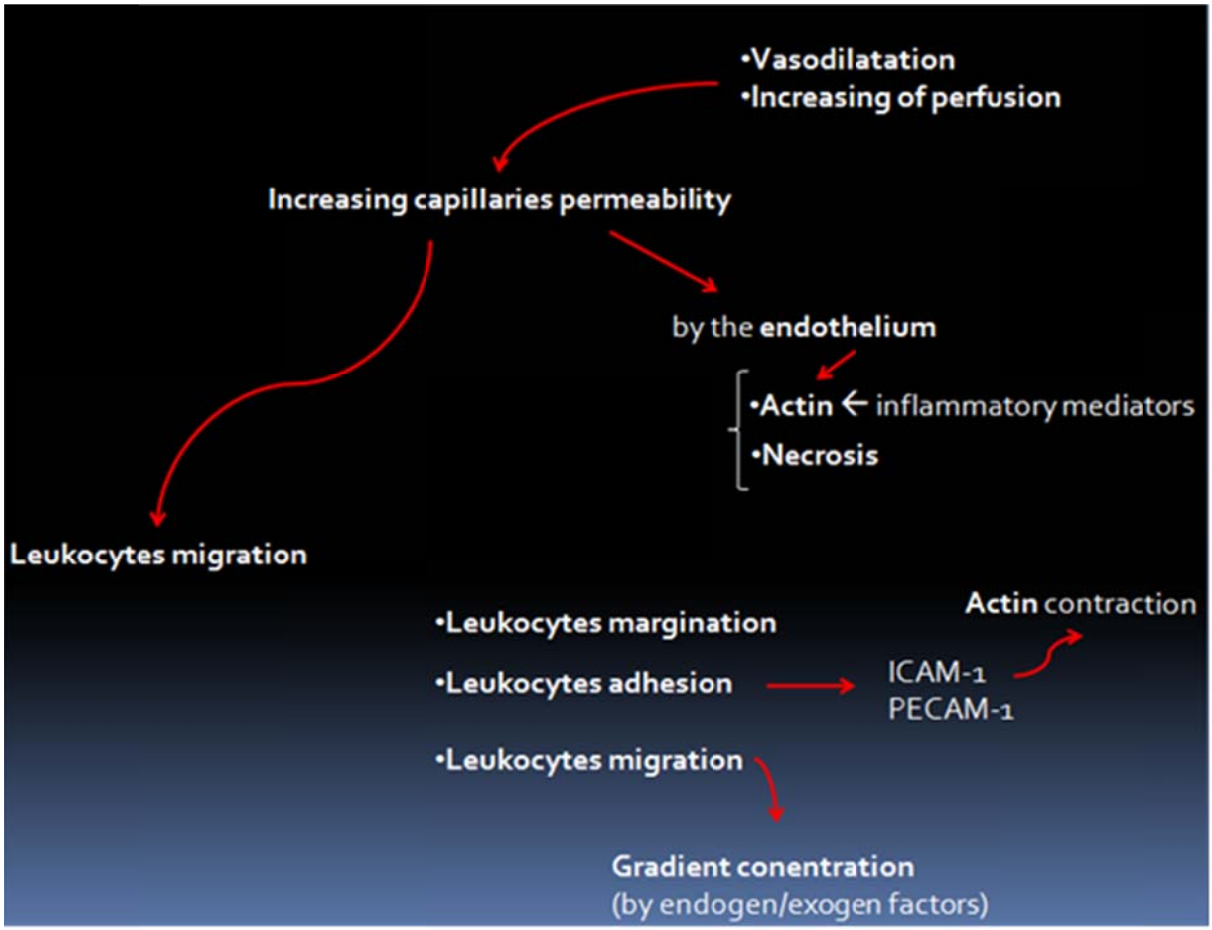

Figure 3. Inflammatory effects

Interleukin - 33

Interleukin-33 (also known as IL-1F11) is a recently found member of the interleukin-1 family (39). It is mainly expressed by epithelial and endothelial cells. This expression is upregulated by pro-inflammatory stimulation, thus contributing to the further amplification of inflammatory responses (40). IL-33 plays an important role in inflammatory diseases as hypersensitive diseases (asthma), autoimmune diseases (rheumatoid arthritis), cardiovascular diseases (heart failure) and neurodegenerative diseases (Alzheimer). Interleukin-33 binds to ST2L receptor which is a kind of toll-like receptor superfamily (39). Interleukin-33 complex consists of ST2 receptor and IL-1 receptor accessory protein (IL-1RAP) and mediates via TIR domain of IL-1RAP (41). The ST2 gene encodes two isoforms: transmembrane ST2L and a soluble form – sST2. IL-33 works in two ways as a traditional cytokine and as nuclear transcription factor.

Interleukin-33 induces the production of many cytokines such as IL-4, IL-13 and activates numerous of cells including Th2, basophils, mast cells. It also increases the concentration of immunoglobulins in the serum (42). Consistent with these observations, IL-33 is a modulator of inflammation, mediating Th2 immune responses.

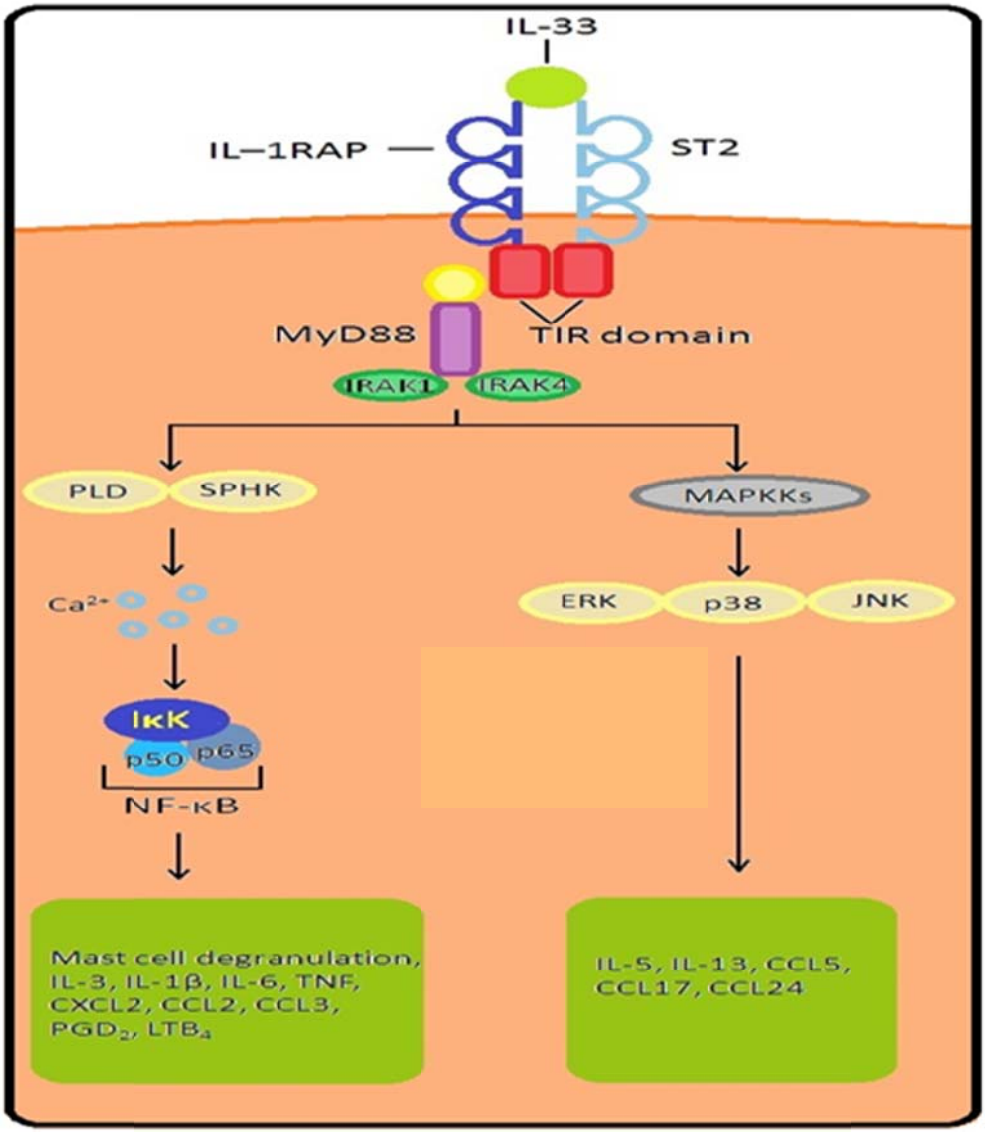

Figure 4. IL-33 signaling pathways.

IL-33 receptor has a heterodimeric structure which consists of ST2; IL-1 receptor accessory protein (IL-1RAP) mediates the response via TIR domain of IL-1RAP. IL-33 binds to this receptor activates the recruitment of MyD88, IRAK1 and IRAK4 to the receptor complex activating NF-κB, IκBα and other various MAPKs.

Modified by authors from Adipogen "IL-33" available on Axxora.com

Interleukin-33 has been found to exert a pleiotropic activity atherogenic and cardioprotective in vivo (43) by inducing Th1–to-Th2 switch and by stimulation the production of IL-5 which increases the level of oxLDL antibodies.

Cardioprotective role starts when IL-33 ligand is bound by ST2L. The IL-33/ST2 complex plays a role similar to the B-type natriuretic peptide (BNP) by protecting the heart from harmful cardiomyocyte hypertrophy (44).

Role of IL-33/ST2 in asthma

As previously mentioned asthma is a chronic inflammatory disease of the airways that involves a very complex cell interaction, mediators, cytokines and chemokines and is associated with variable airflow limitation, superimposed bronchospasm and increased airway responsiveness. Interleukin 33 is a powerful inducer of Th2 cells responsible for the releasing of immune factors involved in the inflammatory response. Some studies have shown that IL-33 concentrations are higher in asthmatics than in healthy subjects (45,46,47).

Recently IL-33 expression has been found in endobronchial biopsies with higher levels in asthmatic patients compared to controls, that was more evident in patients with severe asthma (46). The expression was mainly found in the bronchial epithelial cells (48). Several studies have been conducted to understand which lung cells were more involved in response to IL-33. It was shown that both, endothelial and epithelial cells are important, but not smooth muscle cells or fibroblasts (49). However, experiments conducted on mice by Kurokawa et al, revealed that IL-33 may contribute to the induction and maintenance of eosinophilic inflammation in the airways probably by action on lung fibroblasts (50).

The animal model studies have shown a functionally important role for IL-33/ST2 in asthma and allergic airways inflammation. In a murine ovalbumin-induced airway inflammation model, intranasal IL-33 induced antigenspecific IL-5+ T cells and promoted allergic airway disease even in the absence of IL-4. Intranasal IL-33 promoted also an increased airway responsiveness, polarization of macrophages towards an M2 phenotype, globlet cell hyperplasia, eosinophilia, lung accumulation of IL-4, IL-5, IL-13 (39).

More recently Zhiguang et al created a transgenic mouse in which the IL-33 expression was under the control of CMV (51). The histological analysis showed a very high airway inflammation with eosinophils infiltration around bronchi and small blood vessels, hyperplasia of globlet cells and accumulation of mucus on pulmonary tissue. Also an increased concentration of IL-5, IL-8, IL-13 and IgE was detected in bronchoalveolar lavage fluid (51). In contrast, the research conduced by Liu et al with anti-IL-33 treatment (given intraperitoneally), showed a significant decrease of the serum IgE, the eosinophils and lymphocytes, IL-4, IL-5 and IL-13 (52). Histological examination has shown a significant inhibition of allergen-induced-lung eosinophilic inflammation and mucus hipersecretion (52). Moreover, blockade with anti-ST2 antibodies or ST2-Ig fusion protein, inhibits Th2 cytokine production in vivo, eosinophilic pulmonary inflammation and airways hyper-responsiveness (53). To better understand the role of IL-33 and his receptor ST2 in lung inflammation, different researcher's groups created a mice IL-33-deficient. Oboki et al demonstrated that 2 sensitizations of IL-33 -/- mice with ovalbumin emulsified in alum showed lower lung lymphocyte and eosinophil recruitment, lower airway hyper-responsiveness and inflammation (39). Based on the model used, the disease can be attenuated by acting on IL-33 or ST2, and the data obtained suggest that IL-33 is involved in lung inflammation and ST2 can be used as an asthma's therapy (39, 52, 53, 54, 55). The mechanism of IL-33 action is shown in Fig.5.

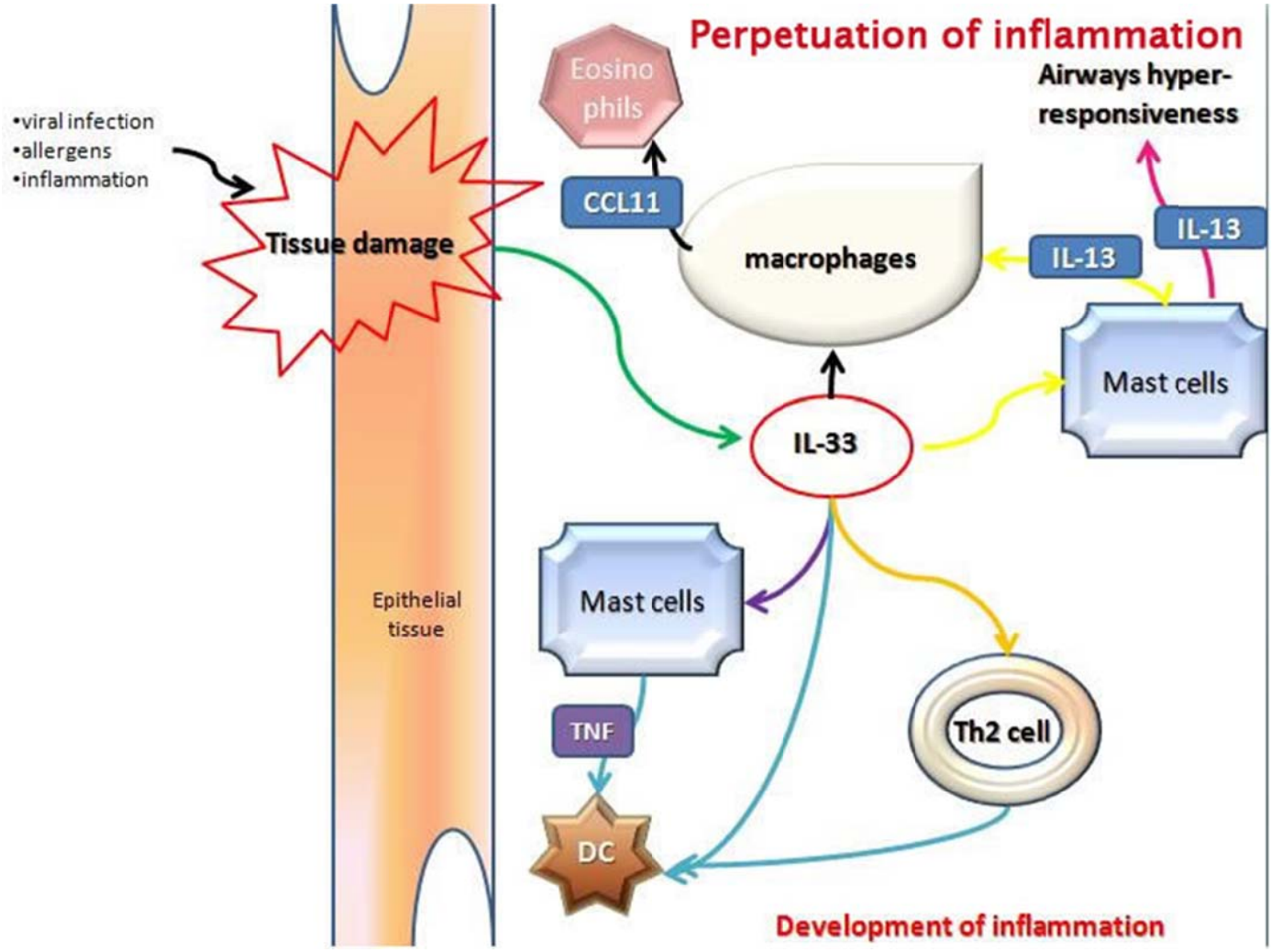

Figure 5. Mechanism of IL-33 interactions.

With the tissue damaging, from infection, contact with allergens or inflammation, IL-33 is released from epithelial cells. IL-33 , during asthma, may stimulate the antigen sensitization and Th2 cells mediated inflammation due to its ability to activate dendritic cells and to recruit and activate Th2 cells. Mast cells activated by IL-33, release TNF-α which helps in the antigen sensitization. IL-33 may induce eosinophilia and higher airway responsiveness by the activation of mast cells and IL-13, activate macrophages and CC-chemokine ligand-11.

Modified by authors from the article of Liew et al. Disease-associated functions of IL-33: the new kid in the IL-1 family. Nature Rev Immunol 2010, 10, 103-10

Role of IL-33 in atherosclerosis.

In a process of atherosclerosis monocytes, mast cells and T cells infiltrate plaques within the intima-media. It was suggested that IL-33 may have a protective function during atherosclerosis process by inducing a switch from Th1 to Th2. Miller et al showed that IL-33 administration to ApoE-/- mice induced Th2 cytokines and protective ox-LDL antibodies, which significantly reduced atherosclerotic plaque development in the aortic sinus (56). Also McLaren demonstrated on a mice model that IL-33 significantly reduces macrophage foam cell formation in vitro in THP-1 macrophages and primary human monocyte derived macrophages (HMDMs) by decreasing acetylated and oxidized LDL uptake, reducing intracellular total and esterified cholesterol content and by enhancing cholesterol efflux (57) . They found out that IL-33 may have potential action in expression of genes involved in cholesterol esterification and triglyceride storage (57).

IL-33 plays a role in patients with obesity and type 2 diabetes which is linked with atherogenesis (58). Recent investigations show the expression of IL-33 and ST 2 in adipocytes and adipose tissue. It was shown that treatment of

in vitro cultured adipose tissue cells with IL-33 induced production of Th2 cytokines (IL-5, IL-13, IL-10) and reduced expression of adipogenic and metabolic genes (C/EBPα, SREBP-1c, LXRα, LXRβ,and PPARγ) (39, 58). Furthermore, treatment of genetically obese diabetic (ob/ob) mice with IL-33 led to protective metabolic effects with reduced adiposity, reduced fasting glucose and improved glucose and insulin tolerance. Additionally, mice lacking endogenous ST2 and fed a high-fat diet had increased body weight and fat mass and impaired insulin secretion and glucose regulation compared to WT controls fed a high-fat diet (39).

The protective effects of IL-33 on adipocytes appear to be mediated via an increased production of Th2 cytokines and a switching of macrophage polarization from an M1 to M2 phenotype (44,64). Moro and Yamada reported a new type of innate lymphocytes present in a novel lymphoid structure associated with adipose tissues in the peritoneal cavity (59). These cells do not express lineage (Lin) markers but do express c-Kit, Sca-1 (also known as Ly6a), IL7R and IL33R.

Similar lymphoid clusters were found in both, human and mouse mesentery, and this tissue was named 'FALC' (fat-associated lymphoid cluster) (59). FALC Lin(-)c-Kit(+)Sca-1(+) cells are distinct from lymphoid progenitors and lymphoid tissue inducer cells. These cells proliferate in response to IL2 and produce large amounts of T(H)2 cytokines such as IL5, IL6 and IL13. IL5 and IL6 regulate B-cell antibody production and self-renewal of B1 cells (59).

CONCLUDING REMARKS

The studies on IL-33 are still running and those already published emphasize the important role of IL-33 in Th2 cell mediated immunity. New data show that IL-33/ST2 pathway is important also in the cardiovascular system. IL-33 seems to have different protective effects on atherosclerosis, obesity, diabetes and also cardiac fibrosis. And that's not eveything; ST2 seems also to be an important biomarker to predict the mortality in presence of different cardiovascular disorders (41). The manipulation of IL-33/ST2 pathway is a promising new therapeutic strategy in the treatment and prevention of many inflammatory disorders.

However, it is important to emphasize that IL-33 the exacts role of this cytokine needs to be further explored. In fact many questions about the biology of IL-33 still need an answer, including the nuclear effect, the processing and releasing of this cytokine from the cells. "The question is how can all the informations derived from in vitro studies and animal models be applied in clinical settings?"(60).

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