

## Pentraxin 3 in Systemic Lupus Erythematosus: Questions to be Resolved

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Systemic lupus erythematosus (SLE) is a autoimmune disorder with unpredictable course that involves polyclonal autoimmunity against multiple autoantigens and presents a broad spectrum of clinical manifestations (fever, skin rashes, arthralgia, inflammation of kidney, lungs, or brain) [1]. The pathogenesis of SLE is based on a combinations of genetic variants and environmental factors that promote loss-of-tolerance or tissue inflammation [2]. In fact there is growing evidence to suggest that inflammation and related molecules plays a key role in the pathogenesis of SLE.

The pentraxin superfamily (PTXs), divided into long and short PTXs, can induce by a variety of inflammation-associated stimuli [3]. Alongside the classical short pentraxins C-reactive protein (CRP) and serum amyloid P component (SAP), pentraxin 3 (PTX3) is a prototypic of long pentraxin family, a multifunctional protein characterized by a cyclic multimeric structure and a conserved domain [4].

An increasing number of studies identified PTX3 as a key component in the host defence against certain infection such as fungal, bacterial and viral [5,6]. Furthermore, higher circulating PTX3 levels have been observed in cardiovascular diseases [7] and above in some autoimmune disorders, such as vasculitis [8], celiac disease (CD) [9] and SLE [10]. Despite of several studies, the literature provides a contradictory picture of PTX3 in SLE patients and, at the moment, have not been yet identified any biochemical markers that allow to accurately monitoring disease activity. Since SLE is characterized by chronic inflammation and immune dysfunction, PTX3 may play a role in the pathogenesis of this disease. Unlike CRP and SAP, PTX3 is produced by resident and innate immunity cells in peripheral tissues, in response to inflammatory signals [11]. However the Literature provides a contradictory picture of PTX3 in SLE pathogenesis and several questions should be resolved. The first issue to be resolved are that the PTX3 are really involved in SLE pathogenesis. In fact it is now known that CRP levels, usually parallel with disease activity in inflammatory states, are often not accompanied by elevated CRP levels [12].

It has been shown that Toll Like Receptor 7 (TLR7) and TLR 9 signalling play a pivotal role in SLE pathogenesis. Very recent study revealed that estrogen receptor  $\alpha$  knockout mice have impaired inflammatory responses to TLR 3, TLR4, TLR7 and TLR 9 ligand stimulation in Dendritic Cells (DCs) [13]. Also data in mice indicate that TLR4 play a key role in mediating autoimmunity, pro-inflammatory cytokine production, and other immune activation. TLR4 is one of the best characterized and the first member of the TLR family [14]. TLR4 signaling is implicated in the innate

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immune responses against a wide-range of microbes, including Gram-negative and -positive bacteria, mycobacteria, spirochetes, yeasts, and some viruses and mammary tumor viruses [14]. TLR4 is implicated in a diverse range of pathological processes associated with autoimmune diseases such as psoriasis, diabetic retinopathy, thrombosis, and inflammatory disorders including arthritis and atherosclerosis [15].

There is evidence of a role of TLR4 in SLE disease pathogenesis, such as the kidney damage, the induction of CD 40 and autoantibodies, the suppression of regulatory T cells, and the role of pro-inflammatory cytokines in SLE pathogenesis [16]. In mouse-model sex hormones could directly change TLR4 responsiveness through several mechanisms. Evidences suggested that NF $\kappa$ B is a focal point in the signal transduction cascades that mediate inflammatory cues from antigen receptors on T cells and B cells, and from TLRs on cells of the innate immune system [16]. Besides hypomethylation-driven activation of NF $\kappa$ B-sensitive genes, other oxidation-induced alterations in transcription factor programmes are implicated in SLE [16].

The corresponding PTX3 human gene are located on chromosome 3 band q 25. The proximal promoter share numerous transcription

factor binding sequences (such as NF- $\kappa$ B) and [17] it was been demonstrated that NF- $\kappa$ B binding site is essential for PTX3 gene transcriptional response. Also PTX3 is produced in response to a variety inflammatory signals mediated by TLR agonists, IL-1 and tumor necrosis factor alpha (TNF- $\alpha$ ) [18]. It was elegantly demonstrated that PTX3 was strictly necessary for NF- $\kappa$ B activation in model of intestinal reperfusion injury and underlined a fundamental role of PTX3 in mediating tissue inflammation under sterile conditions [18]. An integrate viewpoint suggested that PTX3 responsiveness lupus is possible and it could speculated that PTX3 may play a role in SLE pathogenesis. After these hypothesis it should be verify that the PTX3 concentration in SLE patients and the possible link between disease activity: the second issue to be resolved. In Hollan study healthy subjects showed a serum PTX3 level as  $1.21 \pm 0.59$  ng/ml [19]. On the other hand Yamasaki reported the mean plasma PTX3 concentration around 2.00 ng/mL for healthy Japanese people [20]. These different value could be refers to the use of two different matrix (plasma and serum) during the detection of healthy control PTX3 concentration.

Of the 53 healthy controls in Shimada study the mean plasma PTX3 concentration was  $2.2 \pm 1.1$  ng/mL, which was nearly

identical to that of the healthy subjects in Yamasaki's study [20]. Fazzini [21] and Hollan [19] reported serum PTX3 concentrations (not plasma) of 28 SLE patient and three patients with SLE, respectively. The mean serum PTX3 concentration of the 28 SLE patients reported by Fazzini et al. [8], was  $0.38 \pm 0.50$  ng/mL, which was lower than that of  $1.00 \pm 0.47$  ng/mL in their healthy controls. However, 12 of their 28 SLE subjects did not have active disease with SLE activity index (SLEDAI) at zero (SLEDAI=0). On the other hand Kim [22] reported that PTX3 levels were higher in febrile SLE patients but not evaluated SLE patients with active. At the moment it cannot define a single average PTX3 level in healthy subjects and obviously much less in SLE it cannot be define an adequate cut-of point.

These controversial aspect can be resolved by a study with an adequate number of subject in different disease-activity status (SLEDAI score) linked with a careful re-evaluation of the experimental data. An integrated genetics, clinical and basic science viewpoint could be clarify the role of PTX3 in SLE pathogenesis.

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