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Novel molecular targets in the treatment of systemic lupus erythematosus

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Abstract

T cells from patients with systemic lupus erythematosus (SLE) display a number of biochemical abnormalities which include altered expression of key signaling molecules, heightened calcium responses, and skewed expression of transcription factors. These defects are involved in the altered behavior of SLE T cells and are probably central in the disease pathogenesis. The aim of this communication is to review the defects that have been consistently documented in SLE T cells, highlighting molecules and pathways that represent therapeutic targets.

Keywords

autoimmunity; CD3 ζ ; pathogenesis; PP2A; systemic lupus erythematosus; therapy

In patients with autoimmune diseases, the immune system mounts full-scale responses against self constituents; it destroys self tissues using the same mechanisms it relies on when dealing with foreign noxious agents. Accordingly, the therapeutic actions of the drugs designed for the treatment of these conditions –whether conventional or biological– depend on their capacity to inhibit immune effector mechanisms. Thus, different degrees of immune suppression are implicit in their therapeutic capacity. The suppression of the immune system permits patients with autoimmune diseases to live better, longer lives, but is not able to cure them. Although in these conditions immune suppression is evidently useful, its use is always associated with the risk of infectious and malignant diseases.

Patients with systemic lupus erythematosus (SLE) develop an immune response against a variety of ubiquitous antigens. Clinically, it manifests as a waxing and waning inflammatory disease whose intensity and organ involvement varies significantly. High concordance rates in monozygotic twins indicate that genetic factors play a major role in SLE development. In fact, polymorphisms of a number of genes have been linked to SLE. The mechanisms by which such polymorphisms contribute to disease expression are mostly unknown, however, the general assumption is that their presence causes functional changes in the immune response that make the system prone to autoreactivity when exposed to certain environmental or hormonal triggers. The risk imposed by the presence of each of the genetic factors associated

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with SLE is, at the most, moderate. Thus, it is unlikely that the presence of isolated susceptibility alleles is sufficient to cause the disease. Patients must carry combinations of several risk conferring polymorphisms which, when present together, are capable of rendering them vulnerable to SLE development. The former assumption is based on the premise that the susceptibility conferring alleles entail functional repercussions in the cells that express them. Hence, they must manifest as a particular phenotype.

T lymphocytes are crucial for the effector and regulatory arms of the immune response. Extensive evidence has granted them a role in the pathogenesis of SLE [1]. Even though some of the defects described in SLE T cells are probably related to the distinct activation state of the cells at the moment of isolation, others have proven to be intimately linked to the disease itself and absent in the conventional T cell activation process (Table 1). Although it is impossible to demonstrate in a definitive manner to what extent these abnormalities contribute to the expression of the disease, it has been demonstrated repeatedly that their correction by gene transfer or gene silencing or by the simple use of pharmacologic agents results in correction of effector cell function including the production of interleukin-2 (IL-2). It is tempting, and probably appropriate, to predict that correction of immune cell function may result in improvement of organ pathology and subsequent clinical improvement. The aim of this communication is to review potential therapeutic targets that fit the aforementioned description in SLE T cells.

CD3 ζ and FcR γ

CD3 ζ is component of the CD3 complex and represents the main signaling partner of the T cell receptor (TCR). The levels of CD3 ζ are significantly diminished in T cells from most patients with SLE [2]. Paradoxically, the defect is associated with increased calcium influx following TCR-mediated stimulation. The absent chain is replaced by a surrogate molecule normally absent in T cells: the Fc receptor (FcR) γ chain (originally identified as a component of Fc ϵ RI) [3]. The substitution creates an alternative signaling transduction pathway. Instead of relying on ζ -associated protein (ZAP-70), the signal is transferred through Syk (spleen tyrosine kinase), a kinase normally not found in T cells. The resulting association (FcR γ -Syk) delivers a signal ~100 times more intense than the expected by CD3 ζ -ZAP-70. This *rewiring* of the TCR on the surface membrane of SLE T cells, where FcR γ -Syk replaces ζ -ZAP-70, explains the aforementioned hypersensitivity to CD3-mediated stimulation [4]. This has been directly proven with the demonstration that forced expression of FcR γ in normal T cells reproduces some of the changes described in lupus T cells, namely the augmented Ca⁺⁺ response to TCR stimulation and, interestingly, the decrease in the CD3 ζ chain levels [5]. Furthermore, treatment of SLE-derived T cells with a Syk inhibitor (piceatannol 20 μ M) led to the correction of the augmented calcium response and to a significant decrease of several abnormally phosphorylated proteins (Krishnan et al, unpublished). The down regulation of CD3 ζ in lupus T cells is multifactorial, and has been shown to be the consequence of several underlying alterations including decreased transcription [6], decreased mRNA half-life [7], and decreased protein half-life [8] (Reviewed in [9])

The reduction of the ζ chain levels, along with the reciprocal increase in the expression of FcR γ , is directly responsible for some of the phenotypic abnormalities characteristic of lupus T cells [10]. Accordingly, replenishment of the ζ chain leads to the down regulation of the FcR γ chain and subsequently to the correction of the TCR/CD3-induced increased calcium response and the abnormal phosphorylation of cellular substrates [11]. These pathologic abnormalities are specific of SLE T cells and thus represent potentially useful molecular targets. Increasing CD3 ζ levels and/or blocking FcR γ -Syk would be—at least theoretically—a useful means of increasing the activation threshold of SLE T cells.

CD44 and pERM

The molecules that mediate signal transduction in lymphocytes are distributed in a non-random fashion throughout the cell membrane; they are primarily located within zones that are rich in cholesterol and gangliosides. The clustering of key molecules within these regions, called lipid rafts, facilitates their interactions allowing downstream signaling events to occur in a rapid and amplified fashion. When the T cell is stimulated, lipid rafts move and cluster at the zone of the membrane where TCR stimulation is happening. This leads to the concentration of signaling proteins at the immunological synapse.

Membrane morphology and composition are altered in lupus T cells. They possess a larger quantity of lipid rafts, both in resting cells and after stimulation. Moreover, lipid rafts are already clustered in a large fraction of lupus T cells despite the absence of an obvious stimulus [12]. In addition, lipid rafts from SLE T cells exhibit a number of qualitative abnormalities. As mentioned earlier, total CD3 ζ levels are low in SLE T cells. However, the localization of the remaining fraction is altered: an abnormally high fraction is found within lipid rafts [13]. Moreover, apart from CD3 ζ and LAT (which are expected elements), FcR γ , active Syk kinase, and PLC γ 1 are present [12]. These changes have vast functional consequences and are directly linked to the heightened calcium response observed in SLE T cells.

The abnormal signaling pathways used by SLE T cells as well as the pre-clustered lipid rafts that allow faster and greater signal amplification grant an increased inflammatory capacity to the lupus T cell. Accordingly, the altered lipid raft composition outlined before is associated with an increase in the speed of actin polymerization that follows CD3-mediated stimulation (Krishnan et al, unpublished). Further, SLE T cells display an increased ability to adhere and migrate in response to chemotactic factors than T cells obtained from healthy individuals or from patients with rheumatoid arthritis [14]. CD44 is a surface molecule that has been shown to participate in T cell adhesion and migration. It signals through a group of proteins (ezrin, radixin, and moesin; ERM) that become phosphorylated on threonine residues and convey a signal that leads to formation of the uropod. T cells from patients with SLE exhibit increased expression of CD44 and a parallel increase in the phosphorylation of ERM proteins (pERM). Furthermore, CD44, pERM, and F-actin are distributed in a polar fashion in SLE T cells, forming caps that are normally only observed in stimulated cells. Such polar caps are indeed pre-clustered lipid rafts, and their presence depends on the phosphorylation of ERM proteins and the integrity of the cytoskeleton. Hence, treatment of SLE T cells with Y27632, a specific inhibitor of Rho kinase (the enzyme that phosphorylates ERM), disrupts the formation of polar caps and hampers the increased adhesion capacity characteristic of SLE T cells. Addition of cytochalasin D (an actin polymerization inhibitor) or CD44 knockdown (by RNA interference) have shown comparable effects [14]. The importance of the former findings was highlighted by the demonstration that in kidney biopsies from patients with lupus glomerulonephritis, infiltrating T cells expressed CD44 and pERM. In contrast, biopsies from allografts undergoing rejection displayed CD44+ T cells, but lacked pERM expression [14].

pCREB and CREM

A phenotypic hallmark of the T cells from patients with SLE is a failure to produce normal amounts of IL-2 upon activation [15]. Such deficiency could account for a number of abnormalities present in the immune system of SLE patients: hampered T cell responses, defective activation induced cell death, and altered regulatory T cell homeostasis and function.

IL-2 production is primarily controlled at the transcriptional level. The binding of transcription factors to promoter sites of the IL-2 gene is altered in SLE T cells. NF- κ B nuclear activity has been shown to be diminished, and replenishment of the p65 subunit increases IL-2 production in these cells [16]. A consistent finding in the IL-2 promoter of T cells obtained from patients

with lupus has been an imbalance in the CREM/CREB ratio found at the -180 site [17]. The former mainly results because T cells from patients with lupus exhibit abnormally high levels of the inhibitory factor CREM. This abnormality is probably the final common pathway for several of the defects that have been associated to the IL-2 production defect of the lupus T cell. Accordingly, an antisense CREM plasmid is capable of correcting the hampered IL-2 secretion [18].

Numerous factors have been detected in T cells derived from patients with SLE that directly or indirectly affect the balance between CREB and CREM. Interestingly, some of these aberrations appear to be intrinsic to the T cell whereas others reside in the sera of lupus patients. A mechanism by which SLE serum is able to inhibit IL-2 transcription is found on its capacity of activating a kinase called Ca^{++} /Calmodulin-dependent kinase IV (CaMKIV) [19]. We have reported evident alterations in the levels and intracellular compartmentalization of this kinase. Lupus T cells have more CaMKIV and it has been demonstrated that such alteration is a direct consequence of factors present in sera of patients with lupus, particularly those in which anti-CD3/TCR activity is detected [19]. By a still unknown mechanism, lupus-derived sera produce migration of CaMKIV into the nuclei of normal T cells. In the nucleus, this kinase is able to activate CREM and increase its binding to the -180 site. As expected lupus T cells exhibit increased amounts of CaMKIV in the nuclei. The importance of this phenomenon is highlighted by the fact that inhibition of CaMKIV activity by over expression of a dominant negative CaMKIV isoform abolishes the IL-2 inhibiting effect of SLE sera [19].

CREB and CREM are involved in the regulation of other genes and imbalances in their levels alter the expression of several proteins apart from IL-2. c-fos, which assembles with jun to form AP-1, is one of the genes whose transcription is hampered by excessive amounts of CREM. Thus, although alterations of the CREB/CREM ratio probably lead to skewed transcription of a large number of genes, IL-2 transcription is affected by at least two distinct mechanisms: the biased occupation of the -180 site, and decreased AP-1 site occupation [20].

PP2A (protein phosphatase 2A) is a highly conserved enzyme present in virtually all eukaryotic cells [21]. It is the principal enzyme responsible for the dephosphorylation of CREB in T lymphocytes. PP2A levels, measured as protein and mRNA, are abnormally elevated in T cells from SLE patients [22]. PP2A activity is also augmented in lupus T cells and contributes to the defect in IL-2 production by altering the pCREB/CREM ratio. The inhibition of PP2A in lupus T cells (by siRNA or by the expression of dominant negative isoforms) increases pCREB binding to the promoters of c-fos and IL-2 and, by doing so, corrects the IL-2 production defect [22].

Thus, T cells from patients with SLE have a number of alterations that add to blunt –by different mechanisms- their IL-2 producing capacity. Interestingly, most of the pathogenic mechanisms seem to converge in the deregulation of the balance between pCREB and CREM. Some of the defects increase CREM levels, whereas others decrease CREB phosphorylation and thus its capacity to stimulate gene transcription [23].

Potential Therapeutic Targets

The reviewed pathogenic pathways offer a number of potential molecules whose targeting might prove to be of therapeutic value in patients with SLE. As mentioned earlier, some of these molecules act as key mediators in SLE T cells, whilst being completely absent from normal T cells; the levels of others are conspicuously altered in SLE T cells. The targeting of these molecules would, at least in theory, offer the advantage of being relative selective for diseased cells.

The restoration of CD3 ζ chain levels in SLE T cells leads to the correction of a number of their biochemical abnormalities [11]. Thus, CD3 ζ replenishment stands out as a candidate therapeutic goal. As aforementioned, the decline in CD3 ζ levels is a consequence of several pathogenic processes that cannot be easily amended. A feasible means of increasing CD3 ζ expression in T cells could be the decrease caspase-3 activity. As mentioned earlier, the inhibition of this enzyme corrects the defective CD3 ζ expression in SLE T cells. A pan-caspase inhibitor which is currently being tested in patients with liver disease could eventually become a plausible option [24]. An alternative approach is the inhibition of FcR γ -Syk. In fact, Syk inhibition has been evaluated in animal models of rheumatoid arthritis [25]. The major caveat of this approach is that even though its expression and function are pathological in SLE T cells, Syk plays an important physiological role in several other immune and non-immune cells. Further, generalized inhibition of Syk would be especially problematic in patients with SLE because it would interfere with immune complex clearance by monocytes and macrophages. Thus, in order to be an ideal target in SLE, the inhibition of Syk would have to be limited to T cells.

CD44 and its associated signaling pathway is another potential target. SLE T cells have been shown to express higher levels of CD44 and phosphorylated ERM both in peripheral blood and in affected kidneys [14]. CD44 allows activated/memory T cells to exit the bloodstream in inflamed sites. Thus, targeting CD44⁺ cells would probably lead to widespread effects, not specific for SLE T cells. In contrast, pERM has been observed to be present in autoimmune inflammation (lupus nephritis) whilst absent in kidney allograft rejection [14]. The former suggests that inhibiting pERM levels could be beneficial in the lupus scenario. Ex vivo experiments performed with SLE T cells have shown that the inhibition of Rho kinase is indeed able to abolish the increased adherence and migration capacity of SLE T cells [14].

The correction of the altered pCREB:CREM ratio is an important therapeutic goal in patients with SLE. As mentioned above, this alteration results from several abnormalities, including over expression of PP2A and CaMKIV. Thus, inhibition of the activity of these two enzymes and CREM targeting represent potential useful targets.

Concluding Remarks

The pathogenic mechanisms that underlie SLE are slowly being unraveled. As we progress in its understanding, potential therapeutic targets that will allow the design of specific treatments are emerging. Development of agents capable of inhibiting –or increasing– the expression of the mentioned molecules promises to be more effective and less toxic. The question that remains is to which extent the correction of the biochemical abnormalities of SLE T cells will lead to clinical improvement. Experimental evidence suggests it will indeed be effective, but this notion will need to be proved in the in vivo scenario. There are obviously many critical issues which relate to the Mosaic of Autoimmunity, a number of which are already well illustrated in this issue. However, we refer to several recent papers for additional information on the panorama or spectrum of autoimmunity and immunopathology [26–40].

Take home messages

- T cells are central in the SLE pathogenesis.
- The decreased CD3 ζ :FcR γ ratio that characterizes SLE T cells is associated with an abnormal response to TCR stimulation.
- SLE T cells have increased levels of PP2A that suppresses CREB activity.
- Sera from patients with SLE causes activation of CaMKIV that leads to increased binding of the repressor CREM to gene promoters.

- SLE T cells exhibit a number of specific defects that represent potential therapeutic targets.

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Figure 1. The biochemical defects of SLE T cells translate into specific phenotypic characteristics
 The decrease in CD3ζ levels and its substitution by FcRγ-Syk leads to increased calcium response upon TCR stimulation. The former has a number of downstream consequences including altered gene expression (A). Increased ERM phosphorylation by Rho kinase (ROCK) leads to lipid raft clustering and augmented CD44-mediated T cell adhesion and migration.

Table 1

Major Biochemical Abnormalities in SLE T cells

Molecule	Defect
CD3 ζ	Decreased total levels
Fc γ - Syk	Abnormal expression and association with TCR
ERM	Increased phosphorylation
CD44	Increased levels
CaMKIV	Increased activation; increased nuclear levels
PP2A	Increased levels
NF- κ B	Decreased activity
CREM	Increased levels