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HIV protease inhibitors and autoimmunity: An odd, but promising idea

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Dear Editor,

With this letter, we would like to highlight HIV protease inhibitors (PI) capacity to regulate immunological mechanisms and their potential applications in autoimmunity (Fig. 1).

Indeed, HIV PIs can reduce the pro-inflammatory cytokine environment. They decrease the production of IL2, IFNγ and TNFα from activated peripheral blood mononuclear cells (PBMCs) of healthy subjects [1]. Saquinavir inhibits the production of proinflammatory cytokines (*i.e.* IL6, IL1β, TNFα) and potentiate IL10 secretion in the serum and the lung in a mice model of lung injury, suggesting its immunoregulatory potential [2]. Released by apoptotic or necrotic dying cells, HMGB1 acts as a Damage Associated Molecular Pattern (DAMP), by activating TLR2 and TLR4 signaling and thus triggering inflammatory cytokine production. The accumulation of HMGB1 has been involved in various autoimmune diseases [3]. For example, in Systemic Lupus Erythematosus (SLE) patients, disease activity correlates to HMGB1 levels and high levels of this DAMP are also associated with severe form of Systemic Sclerosis (SSc) [4]. Saquinavir could therefore represent an interesting inhibitor of the DAMP-mediated inflammation. Furthermore, HIV PI dampen the cytotoxic activity of T lymphocytes by modulating the immunoproteasome chymotrypsin-like activity and impairing the epitope presentation by MHC I molecules, both in mice [5], and in human cells [6–8]. The immunoproteasome is expressed in hematopoietic cells and *de novo* synthesized in the rest of cells upon various stresses, notably to stimulate antigen presentation [9]. It has been involved in antigen processing for presentation within class I MHC, production of inflammatory cytokines or NFκB activation [10]. HIV PI capacity to down-modulate the immunoproteasome activity seems to be a very promising therapeutic option for autoimmunity. Indeed, immunoproteasome have been involved in the progression of various autoimmune diseases where its blockage alleviates animal models symptoms [11]. Alongside with these effects, HIV PIs have also been reported to block NFκB activation induced by TLR2 and TLR4 activation in human endothelial cells [12]. Ritonavir impairs the proliferation of endothelial cells and reduces the production of pro-inflammatory cytokines (*i.e.* TNFα, IL6, IL8) through the inhibition of the NFκB pathway [13,14].

Our team has recently established that Ritonavir inhibits the inflammatory signaling pathway induced by FasL (CD95L) [15]. CD95 (Fas/APO-1/TNFRSF6) is a transmembrane receptor that belongs to the tumor necrosis factor receptor (TNF-R) family [16]. Its cognate ligand, CD95L, is a transmembrane glycoprotein mainly expressed by activated T lymphocytes and NK cells or in chronic inflammatory disorders by endothelial cells [17]. This membrane-bound ligand acts locally through cell-to-cell contact to kill infected and transformed cells [18]. The extracellular domain of human CD95L can be cleaved by metalloproteases [19], releasing a soluble CD95L (s-CD95L) into the bloodstream. Unlike membrane-bound CD95L (m-CD95L), s-CD95L fails to trigger cell death but instead contributes to aggravating inflammation in chronic inflammatory disorders such as SLE [20,21] and cancers [22–25] by inducing non-apoptotic signaling pathways including MAPK [26], PI3K[21] and NFκB [27]. CD95 harbors an intracellular conserved amino-acid stretch called death domain (DD), which serves as a docking platform to trigger cell death. Upon binding of m-CD95L, CD95 leads to the recruitment of the adaptor protein Fas Associated Death Domain (FADD) through homotypic interactions *via* their respective DD. FADD in turn aggregates the initiator caspase-8 and caspase-10. The CD95/FADD/caspase complex is called death-inducing signaling complex (DISC) [28] and leads to the elimination of cancer cells through an apoptotic mechanism. Conversely, s-CD95L fails to induce cell death but triggers the formation of a non-apoptotic complex termed motility-inducing signaling complex (MISC) implementing a Ca^{2+} response, which inhibits DISC formation and promotes migration of cancer cells [21–23]. To trigger the MISC, CD95 recruits PLCγ1 *via* an intracellular domain different from its DD that we designated CID for calcium-inducing domain. We observed that the inflammatory Th17 cells bathed with s-CD95L undergo an intracellular calcium signal promoting their trans-endothelial migration and their accumulation into the inflamed tissues of SLE patients through a sphingosine 1 Phosphate (S1P) dependent pathway [17]. Modeling analyses revealed that Ritonavir structure is similar to that of the CID peptide bound to PLCγ1 and its incubation with Th17 cells prevented the s-CD95L-mediated inflammatory signal by preventing recruitment of PLCγ1 by CD95. To reach this conclusion, we initially developed a protein-fragment complementation assay (PCA) monitoring the PLCγ1/CD95 interaction and performed a large-scale screen to identify drugs that disrupt this interaction. This approach identified Ritonavir as a potent disruptor of the CD95/PLCγ1 interaction exhibiting no effect on the CD95/FADD interaction responsible for the induction of the apoptotic pathway, which is instrumental in immune homeostasis. Interestingly,

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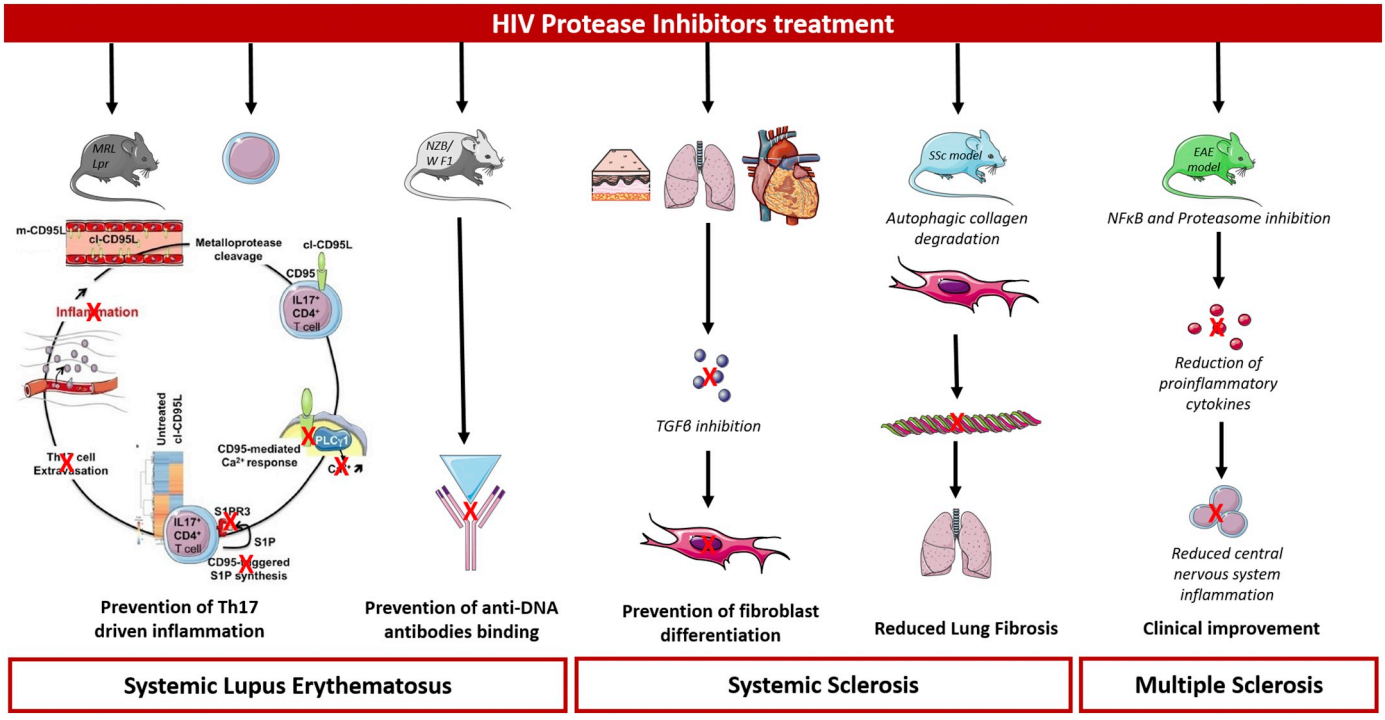

Fig. 1. HIV Protease Inhibitors potential applications for autoimmunity.

administration of Ritonavir in lupus-prone mice dramatically improved the architecture and the function of kidneys as compared to controls [29].

SSc is a rare autoimmune disease characterized by microangiopathy accompanied by fibrosis of the skin and internal organs [30]. Nelfinavir prevents fibroblast differentiation in normal skin, lung and heart and in SSc lung, through the inhibition of the canonical TGF-β pathway (attenuation of Smad3 expression and Smad2/3 phosphorylation) in a dose-dependent manner. Moreover, it increases autophagic degradation of type I collagen in fibroblast by inhibiting the mTOR pathway and reduces lung fibrosis in an animal model of SSc [31] and this could represent a new set of anti-fibrotic drugs for this disease.

In conclusion, HIV PIs reduce DAMP mediated inflammation, inhibit the immunoproteasome and prevent neoangiogenesis. These “off-target effects” are very attractive to envision repositioning them for autoimmune diseases (Fig. 1) and it seems of particular interest to further investigate these drugs and, perhaps, open a new way towards effective therapies for these patients.

Ethical statement

This article contains no clinical data.

Declaration of Competing Interest

This article contains no conflicts of interest.

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