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REVIEW ARTICLE

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Soluble Fas Ligand, an overlooked target of therapy in dermatological and non-dermatological conditions

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ABSTRACT

Background: The Fas/Fas Ligand (Fas/FasL) system mediates key physiological and pathological pathways. Therapies targeting this system are currently unavailable due to the complexity of the Fas/FasL pathway and the side effects associated with reduced apoptosis of cancer cells and the lack of regulation of the immune system. PC111 is a human monoclonal antibody that uniquely targets the soluble (s) but not the membrane-bound (m) FasL, the latter being responsible for immunosurveillance and cancer; the selective mode of action of PC111 precludes its interference with the latter mechanisms. We showed previously that selective blocking soluble FasL (sFasL) could be an effective non-immunosuppressive treatment in mouse models of Pemphigus (PV) and Stevens–Johnson/toxic epidermal necrolysis (SJS/TEN).

Aim: To identify additional diseases where sFasL is elevated and potentially involved in their pathogenesis.

Findings: sFasL is up regulated in drug reaction with eosinophilia and systemic symptoms. Systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and Sjogren syndrome also have elevated levels of sFasL that are involved in some of the mechanisms underlying the diseases. Finally, sFasL is elevated in the bronchoalveolar lavage (BAL) and plasma of Acute Respiratory Distress Syndrome, while blocking sFasL reverses apoptosis in lung epithelial cells, thus reducing mortality.

Conclusion: By selectively blocking sFasL, one could potentially modify the course of several diseases.

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1. Introduction

The Fas Ligand (FasL, CD95L) and its receptor Fas (CD95) are critical components of the tumor necrosis factor (TNF) superfamily, mediating apoptosis (1). FasL is a transmembrane protein that consists of an intracellular domain, a transmembrane section, and an extracellular fragment. FasL ectodomain can be cleaved by ADAM10 protease to release the protein fragment into the extracellular space, called soluble FasL (sFasL) (2). Membrane-bound FasL (mFasL) is primarily expressed on activated T-cells, natural killer (NK) cells, and immune privileged tissues (3). mFasL is involved in homeostatic and regulatory functions, since it typically induces apoptosis by engaging the Fas receptor, thus playing a crucial role in T-cell regulation and cancer (4). The mechanism of action of sFasL is complex and may vary based on local tissue concentrations of ligand and receptor, cell priming, and co-mediators. For example, while sFasL can directly cause apoptosis, it has been proposed in some tissues and disease settings to act as a decoy ligand blocking the action of higher affinity mFasL (5). sFasL has been implicated in a broader range of cellular outcomes, including inflammation, tissue damage remodeling, immune modulation (6–8), and apoptosis, depending on the context and disease state (9–11).

The Fas/FasL system plays a critical role in several conditions. Indeed, multiple defects in the extrinsic apoptotic pathway triggered by Fas/FasL are present in human tumors and contribute to tumorigenesis by inhibiting immune-surveillance (12). The Fas/FasL system is also essential for the killing of self-reactive T cells, thus playing an essential function in autoimmune diseases (13). In fact, mutations of the genes coding for Fas or FasL impede the elimination of auto-reactive T-cells (14), and the failure to convey the apoptotic signal can cause the accumulation of lymphocytes and the development of autoimmune reactions, such as the autoimmune lymphoproliferative syndrome (ALPS) (15). ALPS is a nonmalignant uncontrolled proliferation of lymphocytes associated with a relative high risk of developing lymphomas (16). Mutations in genes coding for Fas or FasL are also detected in both mice (17) and human systemic lupus erythematosus (SLE) (18).

Despite the postulated role of the Fas/FasL pathway in cancer and chronic inflammatory or autoimmune diseases, therapies targeting the system are not currently available. Over the past 30 years, only a small number of patents have been filed on the subject, particularly when compared with the other members of the TNF receptor family and their ligands. The complex Fas/FasL-mediated signaling pathway, the severe side effects associated with the reduced apoptosis of cancer cells, and the lack of immune-surveillance have hindered the development of safe and effective treatments tackling this target (19,20).

To overcome these issues, we propose that selectively targeting sFasL and not mFasL would be an ideal therapeutic strategy not interfering with immune-surveillance and cancer. To this purpose, we have developed a fully human anti-FasL monoclonal antibody

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(mAb, PC111) that specifically recognizes sFasL, without binding mFasL. While mFasL is required for cytotoxic activity and constitutes the guardian against lymphoproliferation, autoimmunity, and cancer, sFasL is not involved in these functions. In particular, mice lacking sFasL appeared normal and their cells could readily kill target cells, whereas mice lacking mFasL could not kill cells through Fas activation (4). *In vitro* experiments show that mFasL is elevated in activated T-cells that rapidly undergo apoptosis. Moreover, PC111 failed to suppress apoptosis in human CD4+ cells, indicating that a limited interference with T-cell functions in immune-surveillance (21).

Elevated levels of sFasL have been detected in a variety of pathological conditions, such as autoimmune disorders (22), cancer (23), and infectious diseases (24). Recently, sFasL has been proposed as an important disease biomarker for clinical application, with the potential of becoming a target of therapy (25). Understanding the functions of sFasL in different disease settings is critical for evaluating its potential as a therapeutic target. In the present review, we aim to discuss sFasL as a possible target of therapy, introducing two examples of its successful blockade by PC111 and evaluating the potential effect of such a blockade in dermatological and non-dermatological conditions.

1.1. Blocking sFasL as a treatment strategy in pemphigus (PV) and Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN)

Despite its ambiguous role in relation to apoptosis and immuno-inflammation, sFasL has been shown to play a crucial role in two different skin conditions. Pemphigus is a chronic autoimmune blistering disease, characterized by the presence in patients' sera of autoantibodies (PVIgG) directed mostly against the adhesion molecules desmogleins 1 and 3 (Dsg1 and Dsg3) located in the inter-keratinocytes junctions (desmosomes) (26). PVIgG cause cell-to-cell detachment (acantholysis), leading to the formation of its characteristic flaccid blisters and erosions in the skin and mucous membranes, including buccal mucosa with feeding problems and weight loss, as well as in the larynx with hoarseness (27). PV is associated with a poor quality of life, further compounded by the severe side effects associated with the use of potent immunosuppressive drugs which are standard of care in patients with this disease; among them, mortality rate ranges between 5% and 30% (28).

sFasL is elevated in PV patients' sera, inducing keratinocyte apoptosis, while anti-FasL neutralizing antibodies block this process *in vitro* (22). sFasL triggers apoptosis by activating caspases that in turn cleave and degrade Dsg, thus inducing acantholysis (29). Blocking FasL by siRNA inhibits caspase activation and Dsg degradation, indicating that FasL plays a critical role in acantholysis *in vitro*. sFasL, but not mFasL is responsible for blister formation in PV. Indeed, injection of PVIgG into neonatal mice lacking sFasL gene fails to trigger blister formation. On the contrary, blisters are still observed in mice lacking mFasL genes and in wild-type animals. PVIgG-induced blister formation in neonatal mice is associated with the early up-regulation and release of FasL in mouse epidermis, while an anti-FasL neutralizing antibody, administered few hours after PVIgG induction, blocks blister formation (30). This result was confirmed in an active *in vivo* PV mouse model that not only recapitulates the complexity of pemphigus but also allows the long-term evaluation of the disease and, thus, the potential effects of experimental drugs. An anti-murine FasL antibody reduced the PV score, counteracted weight loss, and prolonged survival rate in these animals (11). Finally, the fully human mAb PC111, that does not recognize the murine FasL, blocked blister formation in a proprietary, transgenic humanized FasL mouse model of pemphigus that has been developed, indicating that blocking sFasL potentially impedes blister formation also in a human setting (21). This critical experiment carried out in what is considered the "gold standard" model of PV treatment, strongly supports the likely efficacy of PC111 also in PV patients.

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are acute, life-threatening diseases characterized by detachment of the epidermis and mucous membrane. SJS/TEN is a type IV hypersensitivity reaction of different severity caused mostly by drugs; it can also affect lung, liver, and kidneys and is associated with a high mortality rate and long-term sequelae (31,32). The key event in the pathogenesis of SJS/TEN is the activation of cytotoxic (CD8+) T cells that triggers the production of cytokines and chemokines resulting in keratinocyte apoptosis (33). NK cells can also trigger keratinocyte apoptosis and are likely a source of the apoptotic mediator granulysin. Furthermore, drug-activated monocytes may trigger necroptosis of keratinocytes *via* Annexin A1 binding to formyl peptide receptor 1 (FPR1). Several apoptotic mediators are involved in the pathogenesis of SJS/TEN, such as TRAIL, perforin, granzyme, TNF-α, granulysin, and sFasL (34). A strong association has been detected between FasL gene polymorphism and SJS/TEN (35). sFasL levels are consistently elevated in SJS/TEN patients' sera (36–38). In addition, T cells derived from patients with SJS/TEN release high levels of sFasL, when stimulated with the causative drug (39), while patients' sera induce apoptosis in cultured keratinocytes (40). The critical role of sFasL is confirmed using an anti-sFasL monoclonal antibody that dose-dependently prevents SJS/TEN serum-induced cell death in human keratinocytes. Moreover, the administration of PC111 significantly ameliorates conjunctivitis in a mouse model induced by injecting SJS/TEN peripheral blood mononuclear cells plus the causative drug and inhibits apoptosis of the conjunctival epithelium in the same mice (41).

In conclusion, sFasL plays a critical role in both PV and SJS/TEN and PC111, by blocking selectively sFasL, could be a safe and effective therapy for both conditions, potentially leading to a long-term remission in PV and to the blockade of SJS/TEN progression (11).

2. sFasL blockade as a potential treatment strategy in dermatological and non-dermatological conditions

Because sFasL is not involved in the elimination of immune cells by cancer cells according to the 'tumor counterattack' theory (42), it could be hypothesized that its blockade would be beneficial in the treatment of several tumors. While data on the role of sFasL in promoting cancer is still controversial, sFasL has been shown to promote the aggressiveness of certain inflammatory disorders, such as autoimmune diseases (43). Therefore, based on the encouraging results in the previously described skin conditions, we have reviewed a number of inflammatory and autoimmune pathologies which have not been tested therapeutically so far, but where sFasL levels are also elevated and may have an important mechanistic role in promoting disease

2.1. Cutaneous drug reactions

Similarly to the devastating drug reaction SJS/TEN, it appears that other drug-induced skin conditions are associated with elevated

levels of sFasL. It was previously reported that sFasL is a discriminating feature between drug-induced skin eruptions and viral exanthemas, while elevated levels of sFasL were consistently detected in various drug-induced maculo-papular rashes, viral exanthemas and healthy controls tested negative (44).

2.1.1. Drug reaction with eosinophilia and systemic symptoms (DRESS), and drug-induced hypersensitivity syndrome (DIHS)

DRESS and DIHS are used interchangeably to define a severe delayed T-cell-mediated adverse reaction to several medications. DRESS/DIHS is characterized by generalized rash, facial edema, fever, lymphadenopathy, and organ involvement (45). The pathogenesis of DRESS/DIHS involves genetic predisposition, immune dysregulation and viral reactivation (human herpes virus-6, HHV-6, cytomegalovirus), the latter being responsible for most relapses following acute onset. Mortality rate is up to 10% (46). The treatment of DRESS/DIHS consists of the rapid withdrawal of the culprit drug and the use of immunosuppressive therapies (47). Increased levels of sFasL have been detected in the sera of patients with DIHS (48). Yang et al. found that sFasL was significantly overexpressed in the sera and skin of DRESS patients. Furthermore, the levels of sFasL correlated with the level of liver enzymes in the same patients, indicating that sFasL could play a role in the pathogenesis of DRESS and may be involved in liver function damage that is a major cause of death in such patients (49). Given its rapid mode of action, we feel that PC111 could potentially be a beneficial and, in some cases, life-saving therapy for DIHS/DRESS patients. In addition, its non-immunosuppressive mechanism of action (11) would theoretically avoid the risk of reactivating HHV-6 or cytomegalovirus.

2.2. Autoimmune diseases

2.2.1. Systemic lupus erythematosus (SLE)

SLE is a systemic, multiorgan autoimmune disease that also affects skin and mucous membranes (50,51). Patients with SLE frequently develop hematological conditions and renal disease (52,53). Evidence suggests that FasL, may play a role in SLE pathogenesis. Signaling by FasL through Fas leads to apoptosis, and impaired activation-induced cell death caused by mutations in mouse genes encoding for Fas (lpr) and FasL (gld) leads to spontaneous mouse models reminiscent of human SLE (54,17). The treatment of SLE relies on corticosteroids, other immunosuppressants (55) and hydroxychloroquine (56). The main goal of treatment is to reduce or avoid the use of immunosuppressive drugs often associated with severe side effects (57). Belimumab (anti-B cell activating factor mAb) is the only biotherapeutic approved for the treatment of the non-renal form of SLE (58). The use of Belimumab in combination with standard therapy seems to improve the quality of life of patients with SLE, but it is still an immunosuppressive treatment.

SLE patients display high amounts of sFasL. While IL-17A and IL-17F have been shown to play a critical role in autoimmune diseases (59,60), patients exhibit significant infiltration of Th17 lymphocyte secreting cytokines in their skin (61). In this context, sFasL has been shown to be involved in promoting trafficking of Th17 into damaged organs (62). Tauzin et al. examined the biological effects of sFasL on Fas-sensitive activated T-lymphocytes. They demonstrated that cleaved FasL is increased in sera of SLE patients as compared to that of healthy individuals (63). This finding was confirmed by several reports where sFasL levels are markedly increased in SLE patients without triggering an apoptotic signaling (64,65). In these papers, it is hypothesized that high levels of sFasL may be related to the aggravation of the disease and that a therapeutic strategy should be developed to target sFasL. Because PC111 selectively blocks sFasL, but not mFasL, it may be considered a potential targeted therapy for SLE.

2.3. Organ-specific autoimmune diseases

2.3.1. Rheumatoid arthritis (RA)

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease affecting 1% of the general population worldwide (66). RA involves synovial joints causing pain, disability, and reduced quality of life. RA is a symmetric polyarticular arthritis, primarily affecting small joints of hands and feet, where a persistent inflammatory reaction takes place, leading to bone and cartilage destruction. The pathology of RA is a massive hyperplasia of synovial membranes caused by hyperproliferation of fibroblast-like synoviocytes (67). Treatment relies on disease-modifying anti-rheumatic drugs (DMARDs), a heterogeneous class of drugs including methotrexate, leflunomide, hydroxychloroquine and sulfasalazine. These agents induce disease remission by acting as immunosuppressors, thus blocking autoimmunity and preventing joint degeneration. Further treatment strategies are based on targeted therapies, TNF-α inhibitors, and B-cell depleters, such as rituximab, being the most used biological therapies (68). Though DMARDs and TNF-α blockers are very efficient, one third of the RA patients are unresponsive or present side effects. High levels of sFasL have been detected in the joints and synovial fluids of patients (69). In RA, the apoptotic pathways involving Fas/FasL are defective, while the Fas/FasL system plays an inflammatory role (70) and stimulates synoviocyte proliferation (71). Targeting sFasL with blockers such as PC111, with a non-immunosuppressive mode of action, could be a promising treatment strategy, differentiating itself from the current therapies by avoiding the serious adverse events associated with a protracted use of those drugs.

2.3.2. Sjogren's syndrome (SS)

Sjogren's syndrome (SS) is a systemic autoimmune disorder affecting 0.5–1% of the general population. SS commonly presents with dryness involving the eyes and mouth, due to inflammation of the lacrimal and salivary glands. Up to one-half of affected individuals also develop extra-glandular involvement in organs such as the joints, skin, lungs, gastrointestinal tract, nervous system, and kidneys (72). This condition is frequently associated with other autoimmune disorders, including RA and SLE. Despite great progress has been made in the past 10 years in understanding the pathophysiology of SS, opening new avenues toward a more targeted and individualized therapeutic approach, treatment still relies on the management of dryness, saliva substitute and ocular tears, and on the use of immunosuppressive agents for patients with systemic involvement (73). These include glucocorticoids, methotrexate, leflunomide often in association with hydroxychloroquine (74). Although the role of the Fas/FasL system in SS has been questioned, based on the ambiguous role of sFasL in inducing apoptosis (75), sFasL levels are significantly elevated in saliva and sera from SS patients (76,77) and its blockade in the periphery and in sera could possibly reduce the symptoms and the spreading of SS to extra-glandular organs.

2.4. Acute respiratory distress syndrome (ARDS)

Acute respiratory distress syndrome (ARDS) is characterized by acute, life-threatening hypoxaemic respiratory failure induced by several predisposing factors, including pneumonia, trauma, burns, and multiple transfusions. It is characterized by non-cardiogenic pulmonary edema and increased alveolar–capillary membrane permeability (78). In addition, the majority of patients with severe COVID-19 present similar signs and symptoms. Although there are similarities and differences between COVID-19 ARDS and ARDS due to other causes (79), ARDS is the first cause of death in these patients (80). It is estimated that 10% of ICU patients have ARDS with an incidence of ~10–86 cases per 100,000 person-years (81). Mortality rates are consistently reported as greater than 30%, more often associated with sepsis and multiple organ failure in addition to severe respiratory distress (82). Supportive care and ventilatory support are the mainstay of ARDS treatment, while there is no approved drug for this life-threatening condition (83). Lung inflammation underlying ARDS is associated with increased alveolar endothelial and epithelial permeability (84). Epithelial damage caused by apoptosis is a critical event in acute lung injury (85). Among other factors, sFasL has been shown to induce epithelial cell death in ARDS. Matute-Bello et al. have shown that sFasL is present in bronchoalveolar lavage (BAL) fluid of patients before and after the onset of ARDS, and that BAL concentration of sFasL was significantly higher in patients who had died. In addition, BAL from ARDS patients caused apoptosis of lung epithelial cells expressing Fas *in vitro* and in animal models. This effect was blocked by using an anti-FasL antibody (86). Furthermore, pulmonary edema fluid from patients with ARDS has higher concentrations of sFasL compared to hydrostatic pulmonary edema. Both Fas and FasL are widely present in lung tissue from patients with ARDS (87). These findings were confirmed by the work of Stapelton's group, showing that ninety ARDS patients presented elevated levels of sFasL in BAL and plasma. Mean plasma levels in survivors from ARDS were 50% lower than at baseline (88). Taken together, these data point to a critical role of sFasL in the mechanisms underlying ARDS. sFasL levels are upregulated early in the lungs of patients with ARDS, before clinical onset and during the exudative phase, making it a promising biomarker of the disease. Measuring sFasL in ICU patients suffering from acute pulmonary distress of any kind could allow an early intervention with agents such as PC111 that has been shown to have a rapid mode of action. Therefore, we hypothesize that early and rapid sFasL blockade could become a life-saving strategy for patients with this mortal condition.

3. Conclusions, perspectives, and limitations

Despite the critical role of the Fas/FasL pathway in the pathomechanisms underlying several conditions, including cancer and autoimmune disorders, there have been few attempts to develop therapeutic strategies targeting this system. To our knowledge, the recently studied Fas-Fc fusion proteins have failed because of the low-affinity and the limited efficacy in inhibiting cell death induced by ligand interaction with Fas (89). An 84 kDa FasL neutralizing CD95 trimer fusion protein is currently being developed for patients with glioblastoma multiforme, where FasL is involved in its growth, invasiveness and migration. The extracellular domain of human Fas and the Fc domain of human IgG1 was designed to specifically bind FasL, thus disrupting the Fas/FasL signal, and reducing tumor invasiveness (90). Indeed, a prolonged survival was observed in these patients in a phase II controlled clinical trial (NCT01071837). While these strategies are aimed to specifically bind FasL, they do not distinguish between sFasL and mFasL. This difference is critical in our view to avoid interference of any drug with the immunosurveillance in tumors and autoimmune diseases. PC111, is a human monoclonal antibody that selectively binds sFasL, but not mFasL, thus allowing to target the diseases where the soluble form of the ligand plays a crucial role. That is why, after an accurate analysis of the literature, we have focused on the very few conditions where sFasL blockade with agents such as PC111 could be beneficial and safe, without affecting the important, regulatory functions of the Fas/FasL system (Table 1).

Table 1. Dermatological and non-dermatological conditions with a likely pathogenic involvement of the Fas/FasL system.

Disease	Epidemiology	Rationale
Drug-induced hypersensitivity syndrome (DIHS)/drug reaction with eosinophilia and systemic symptoms (DRESS)	• Incidence: 0.9–40/100.000 • 10 cases/million in the general population • Prevalence: 2.18/100.000 • Mortality: 4–10%	• High sFasL levels in patients' sera correlating with disease severity and liver damage
Rheumatoid arthritis (RA)	• 1% general population worldwide	• High sFasL levels in joints and synovial fluids • sFasL stimulates synoviocyte proliferation
Systemic lupus erythematosus (SLE)	• Incidence: 4/100.000 persons/years in US and EU • Prevalence: 48-366/100.000 in US; 30–70/100.000 in EU • Mortality rate: 13–28 per 1000 person-years	• sFasL levels are markedly increased • High sFasL is related with active disease
Sjogren syndrome (SS)	• Incidence: 0.5–1% general population	• High sFasL levels in in saliva and sera • No correlation with disease severity
Acute respiratory distress syndrome (ARDS)	• Incidence: 10–86 cases per 100,000 person-years • 10% ICU* patients have ARDS • Mortality up to 30%	• High sFasL levels in plasma, bronchial lavage, and lung tissue • Correlation between sFasL levels and death

*ICU: intense care unit.

Our evaluation of sFasL neutralization in models of PV and SJS/TEN and our review of the published literature strongly support the notion that there are multiple syndromes that show acute inflammatory flare with associated apoptosis of membrane or barrier cells. These cells are frequently of epithelial (keratinocyte, conjunctiva, alveolar, and glandular) or other origin such as synovium and may be particularly sensitive to locally elevated levels of sFasL leading to severe tissue injury and organ failure.

It remains to be determined whether sFasL is mechanistically involved in the diseases described above or if it is just a bystander. We were able to convincingly prove that sFasL plays a critical role in PV and SJS/TEN, and that PC111 blocks both disease progression in validated pre-clinical models of such diseases using both wild-type and FasL humanized mice. To demonstrate the pathogenic role of sFasL in other conditions, a well-established animal model is needed. Notably, in most of the indications selected above, a reliable animal model is available for studying their pathogenesis and testing potential drugs (91–95). The availability of a humanized mouse expressing human FasL constitutes a great

opportunity for applying these diverse, specific disease models to test sFasL blockade with agents such as PC111 and/or its derivatives in such a humanized, proprietary platform.

Author contributions

Roberta Lotti: Conceptualization, Writing – Original draft preparation. Brydon Bennett: Conceptualization, Writing – Original draft preparation. Alessandra Marconi: Conceptualization, Supervision. Antonino Amato: Conceptualization, Methodology, Writing – Original draft preparation. Carlo Pincelli: Conceptualization, Supervision, Writing – Original draft preparation.

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Ethics statement

Not applicable.

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Data availability statement

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