Review

Pathogenesis of primary Sjögren’s syndrome beyond B lymphocytes

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ABSTRACT

Primary Sjögren’s syndrome (pSS) is a chronic autoimmune disorder affecting exocrine glands of the body, prevalently lacrimal and salivary glands. The pSS pathogenesis has been thought to be B-cell-centric and several clinical trials have been carried out in order to clarify the therapeutic role of B-cell depletion in patients with pSS. Unfortunately, however, B-cell depletion with rituximab has failed in demonstrating any significant results in pSS patients. Besides the contribution of B cells in the pathogenesis of pSS, effector Tfh, Th17 and Th22 cells, follicular dendritic cells (DCs), innate cells (ICs) and several cytokines, chemokines and miRNA have been proved to participate to the development of this systemic disease. Understanding these molecular processes may help guide research into resistant diseases and highly targeted therapeutic strategies. This review aims to discuss important pathogenetic mechanisms involved in the initiation and perpetuation of pSS behind the established role of B cells.

Introduction

Primary Sjögren’s syndrome (pSS) is a chronic autoimmune disorder affecting exocrine glands of the body, prevalently lacrimal and salivary glands (SG). For long time pSS pathogenesis has been thought to be B-cell-centric on the basis of the evidences that several cytokines and immune cells stimulate aberrant B-cell maturation, leading to the emergence of self-reactive, locally producing autoantibodies, B cells. On the basis of these premises, several clinical trials have been carried out in order to clarify the therapeutic role of B-cell depletion in patients with pSS. Unfortunately, however, B-cell depletion with rituximab has failed in demonstrating any significant results in achieving an improvement in dryness, pain and patient’s global assessment of disease activity (1).

Besides the contribution of B cells in the pathogenesis of pSS, effector T helper cells, follicular dendritic cells, innate cells and several cytokines, chemokines and small molecules have been proved to participate to the sub-version of glandular architecture and to the development of systemic disease. Furthermore, the growing understanding of the relationship between innate immune response and the microenvironment may help to unravel the molecular processes underlying the pathogenesis of the disease and the development of pSS-associated lymphomas. This review aims to discuss important pathogenetic mechanisms involved in the pathogenesis of pSS behind the established role of B cells. In the first part, an overview of structural non-immune cells and cells of the innate immune response (dendritic cells, macrophages, NK cells and innate lymphoid cells) involved in pSS pathogenesis is provided. Subsequently, we have highlighted the role of T cells.

Structural non-immune cells

Endothelial cells

Endothelial cells (ECs) are involved in tissue and organism health and homeostasis and participate in different systemic autoimmune diseases (2-8). The formation of new blood vessels (neoangiogenesis) has been recognised as a key event in the induction and maintenance of systemic autoimmune disease by promoting the tissue recruitment of circulating lymphocytes. An enhanced neo-angiogenesis in pSS salivary glands (SG), correlated the severity of the inflammatory lesions, has been observed and associated with an increased...
VEGF-A expression and activation of VEGF-A/VEGFR2 signalling (9, 10) (Fig. 1). Sisto et al. found a relation between VEGF-A production, VEGFR2 activation and pSS antibodies, demonstrating that anti-Ro/SSA antibodies increased VEGF-A expression and triggered upregulation and activation of VEGFR2. The role of new formed vessels in pSS in promoting and sustaining SG inflammation is supported by the over-expression of adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), E-selectin, ELAM-1 (11-13). Increased expression of ICAM-1 and LFA-1 mRNA have been also observed before the onset of inflammatory SG lesions in MRL/lpr mice. Antibodies to ICAM-1 in combination with anti-LFA-1 prevented adoptive transfer of SS in MRL/lpr mice into SCID mice (14). Disruption of endothelial barrier function, mainly mediated by IFN-γ, is linked with hyposecretion and lymphocytic infiltration in SG of pSS (15). Furthermore, endothelial cells in pSS produce pro-inflammatory cytokines involved in the inflamed process such as IL-17 (16,17), IL-33 (18), TSLP (19), TGF-b (20). Aberrant expression of cytokine receptors, such as IL-22R1 (17), and chemokines such as CXCL13 and CXCL21 and endothelial microparticles (21) have been also demonstrated in pSS ECs. In particular, the ectopic expression of BCA-1 (CXCL13) on ECs and within GC-like structures, together with the strong expression of SDF-1 (CXCL12) on ductal epithelial cells, has been proposed to contribute to the progressive organisation and maintenance of perilobular foci and the excessive production of high-affinity, class-switched autoantibodies and to the high incidence of B cell lymphomas classically associated with pSS (22, 23).

Epithelial cells
pSS has been often referred to as autoimmune epithelitis (24), based on the evidence supporting the central pathogenetic role of the salivary glandular epithelial cells which are the target cells in the initiation of the autoimmune responses. In pSS, SGEC are in fact activated as demonstrated by the increased expression of CD40 and adhesion molecules, and the augmented production of cytokines and chemokines. Activated SGEC are capable to drive the accumulation of DCs, T cells and B cells in the inflamed SG by expressing high levels of cell homing molecules and HLA (25). Significant alterations in the expression and distribution of epithelial tight junction proteins have been detected in patients with pSS, being ZO-1 and occludin strongly down-regulated and claudin-1 and claudin-4 overexpressed. These alterations seem to be dependent by pro-inflammatory cytokines such as TNF-α, IFNγ, IL-17 and IL-18 that may act in a autocrine and paracrine ways (26). A constitutive epithelial cells expression of various immunomodulatory molecules derived from pSS patients has been proved possibly driven by micro-environmental factors. The implication of an epitheliotropic infectious agent, remains a strong possibility representing a possible starting factor for the activation of epithelial tissues and the development of the disease. Epstein-Barr virus (EBV) infection of SGEC has been demonstrated in pSS, by LMP-2A expression in ductal and acinar epithelial cells of pSS. The SGEC infection by EBV could directly contribute to the pathogenesis of pSS by inducing the expression of selected IFN-regulatory factors (IRFs), such as IRF5 and IFN-stimulated genes (ISGs). The resulting chronic activation of SGEC may lead to epithelial apoptosis that in turn may perpetuate the glandular inflammatory processes. Dysfunctions in the SGEC apoptotic pathways in pSS, mainly characterised by the hyperexpression of several apoptotic proteins such as Fas, Fas-ligand, and Bax and the downregulation of Bcl-2 and the apoptosis-related activation of caspase-3 have been demonstrated (27). SGEC have been also demonstrated to drive the activation of NK cells which is correlated with the severity of the exocrinopathy. B7H6, the ligand of the NK receptor NKp30, is in fact expressed by SGEC, suggesting that NK cells would be activated by ligation of their activating epithelial receptors recognising stress-induced molecules in the damaged tissues (27).

Follicular dendritic cells and bona-fide stromal cells
Follicular dendritic cells (FDCs) are stromal cells located in primary follicles and in germinal centres (GC) of secondary and tertiary lymphoid organs where they have the distinctive ability to retain native antigen in B-cell follicles for months (28, 29). In pSS, the inflammatory infiltration in SG is predominantly composed of peri-ductal aggregated of CD4+ T cells, CD8+ T cells, B cells and plasma cells. However, in a subset of patients, lymphoid infiltrates in the SG form ectopic lymphoid organ structures comprising distinct B and T cell compartments, high endothelial venules (HEV), and FDC networks (30-32). FDC, localised in the centre of lymphoid focal structures in labial SG of pSS, expressed CD35, CD11c, and CD106 (VCAM-1), but they did not express either CD14 or CD11b, VLA-2 alpha and VLA-3 alpha, indicating that they may not be of myeloid origin (33). Although this evidence suggests the possibility of acting on FDC to treat pSS, a recent clinical trial assessing the efficacy of a lymphotoxin β receptor IgG fusion protein, Baminercet, which lead to FDC ablation, failed to significantly improve glandular and extraglandular disease in patients with pSS (34). Resident fibroblasts, pericytes and mesenchymal stem cells are poorly described cell populations and have recently been characterised in the pSS pathogenesis.

Dendritic cells or T cells activate the resident stromal cells, via the secretion of pro-inflammatory cytokines (35). Consequently, ECs expression of cell adhesion (ICAM-1,VCAM-1) is amplified, leading to lymphocyte infiltration. Reduction in morphology and function of pericytes, myoepithelial cells present in the vasculature, in diseased compared to control lacrimal glands have also been described (36).

Cells of the innate immune response
Many types of innate cells have been described to be activated in pSS possibly participating to the pathogenesis of the disease. DCs, macrophages, NK cells
and innate lymphoid cells are well studied subsets of immune players in pSS.

**Gamma delta T cells**
Gamma delta T (γδT) cells are non conventional T cells expressing γδ-TCR that are enriched in epithelial and mucosal tissues where they are thought to serve as the first line of defense against pathogens. γδT cells are expanded in the peripheral blood of pSS patients (37-40) and they are able to induce B cells to secrete immunoglobulins, particularly in presence of IL-2 (40). Differently form peripheral blood, γδT cells are significantly expanded in the SG of pSS and are activated and produce high levels of IL-17 and IL-36α (41). IL-36α, which is overexpressed in the serum and SG of pSS patients, expands both IL-17+ γδ T cells and IL-17+ αβ T cells (42). Beyond IL-36α, the plasticity and the effector functions of γδ+ T cells appear to be also regulated by the miRNA 146a/NOD1 axis (43), which expression has been proved to be associated with the risk of pS in a recent meta-analysis (44).

**MAIT cells**
MAIT cells are a recently identified class of innate-like lymphocytes exhibiting restricted T cell receptor (TCR) diversity with important roles in microbial defense (45). Recently, MAIT cells were demonstrated to be significantly
decreased in the peripheral blood, displaying an immature phenotype, but not in the SG tissue from pSS patients (46). Furthermore, residual peripheral blood MAIT cells in pSS patients showed altered immunophenotype and function. While MAIT cells from controls were almost exclusively CD8+ and expressed an effector memory immunophenotype, in pSS patients they were enriched in CD4+ and naive subpopulations expressing low level of activation markers CD69 and CD40L (46). Interestingly, MAIT cells from SG of patients with pSS are IL-17 polarised being this polarisation mediated by two different cytokines, IL-7 and IL-23 (73).

**iNKT**

Few data have been published on iNKT, a subset of T cells playing an important role in regulating immune responses, in pSS. Controversial data have been published regarding iNKT behaviour in pSS. Kojo et al. (48) found that NKT cells were selectively reduced in patients with autoimmune diseases possibly due to an inadequate amount of alpha-GalCer-like natural ligands for the induction of NKT cells in vivo, or to a dysfunction in the NKT cells themselves. Conversely, Guggino et al. (49) found that, in pSS iNKT are expanded in peripheral blood and are functional active since they were able to produce IL-17 and IFN-γ after α-GalCer in vitro stimulation. Although iNKT have been demonstrated to be expanded in the SG of aly/aly mice with pSS (50) they were never detected in the SG of pSS patients (49).

**Innate lymphoid cells**

Innate lymphoid cells (ILCs) are important cells regulating the barrier homeostasis. ILCs are divided into three groups, namely group 1 ILCs, group 2 ILCs and group 3. ILCs, based on the transcription factors they depend on for their development and function and the cytokines they produce. A recent study from Ciccia et al. showed that IL-25 implicated in the regulation of innate lymphoid type 2 immune responses (51). In this study, the IL-25 axis was activated in pSS and experimental Sjögren’s syndrome (ESS) and associated with the increased frequency of IL-25-responsive inflammatory ILC2 cells and M2 macrophages, and production of pSS-related anti-SSA autoantibodies. The pathogenic role of ILC2 in pSS, is also supported by the recent demonstration that TSLP, another cytokine involved in the differentiation of ILC2, is over-expressed in the SG and serum of pSS (19). However, epithelial cells which are likely to account for most of TSLP production.

In a recent study, a significant expansion of NKp44+ ILC3 mainly producing IL-22 has been also demonstrated in the SG of pSS and their percentage was directly and strongly correlated with the severity of tissue inflammation (52).

**Dendritic cells**

Dendritic cells (DC) can be divided into resident lymphoid tissue DC and migratory non-lymphoid tissue DC (53). Classically, circulating DCs are divided in two main subsets: myeloid DC (mDC), which are potent antigen-presenting cells, and plasmacytoid DC (pDC) which are the main type I interferon-producing cells (54). An increased number of infiltrating pDC has been demonstrated in pSS, correlated positively with the macrophage infiltration rate, occurrence of SG enlargement, and presence of C4 hypocomplementaemia, and inversely with serum C4 complement levels (55).

The presence of interferon (IFN)-signature, defined as high expression of a panel of type-I IFN induced genes, has been reported in pSS and the presence of pDC in SG of SS patients as well as the presence of IFN-α-producing cells (56, 57). In pSS, autoantibodies to RNA-binding proteins, combined with material released by necrotic or late apoptotic cells, are potent inducers of IFNα production in pDC (56). This appeared to be attributable to RNA-containing immune complexes triggering pDC by means of RNA and interaction with Fcγ receptor IIa. An hypothesis is that a viral infection triggers the generation of epithelial cell-derived apoptotic particles that can carry SS-autoantigens and consequently activate local pDC located in SG. pDC, stimulated via TLR by the nucleic acid, might produce pro-inflammatory cytokines as IFN-α also enabling the activation of autoreactive T and B cells (58-61).

**Monocytes-macrophages**

Monocytes/macrophages are one of the main cell types involved in the innate immune response (62). Monocyte chemoattractant protein-1 (MCP-1/ CCL2), one of the key chemokines that regulate migration and infiltration of monocytes/macrophages in the tissues, is elevated in the saliva of patients with pSS (63) suggesting an active tissue recruitment of these cells in the inflamed SG. In MRL/Mp-lpr/lpr (MRL/lpr) mice, that spontaneously develop destructive inflammation of the SG and lachrymal glands, maximum levels of macrophage infiltration was seen at 4 months of age, indicating a role for these innate cells in the perpetuation rather than the initiation of the disease (64). In other mice models of pSS, systemic depletion of macrophages had no effect on ocular phenotype but led to significant improvements in lacrimal gland exocrinopathy and tear secretion (65). Inflamed SG from patients with pSS manifest increased infiltration by IL-18-producing macrophages, particularly in B cell-rich areas and in GC-like structures in pSS (55). High infiltration by macrophages in pSS correlate with SG enlargement and the rate of infiltration by IL-18-expressing cells correlated positively with biopsy focus scores, larger infiltrates of macrophages, DCs and B cells, and SG enlargement, and negatively with serum C4 complement levels (55). In this regard, IL-18 dependent aberrant expression of IL-22R1 was observed only among tissue and circulating myeloid cells of pSS patients and macrophages of non-Hodgkin’s lymphoma tissues of pSS patients. IL-22R1 expression on PBMC of pSS was functional, as its stimulation with recombinant IL-22 significantly up-regulated the expression of STAT-3, IL-17 and IL-22 (17). Interestingly, monocytes isolated from pSS patients show an increased expression of VIPAC2 subtype of VIP receptors with an impaired phagocytosis of apoptotic epithelial cells, independent by VIP (66).
pSS often develop in post-menopausal women, even though the mechanism by which estrogen deficiency influences autoimmunity is unknown. Iwasa et al. used a female aromatase gene knockout (ArKO) mice as a model of estrogen deficiency to investigate the molecular mechanism underlying the onset and development of pSS (67). Inflammatory lesions in the lacrimal and SG of ArKO mice increased with age. A significantly increased monocyte chemotactic protein-1 mRNA expression of the salivary gland tissue in ArKO was found together with adiposity and the autoimmune lesions and were exacerbated by administration of an aromatase inhibitor.

In pSS SG, increased numbers of mature monocytes showing the phenotype CD14lowCD16⁺ have been observed and patient and mouse data support a model where this mature monocyte subset migrates to the SG and develops into DC (68). Another subset, CD14highCD16⁺, has been described in the periductal inflammatory foci of inflamed SG of pSS accompanied by overexpression of IL-34 (69). Ro52, an IFN-inducible protein of the tripartite motif (TRIM) family that is an autoantigen in patients with pSS has been demonstrated to ubiquitinate both in vivo and in vitro IRF8. Ectopic expression of Ro52 enhanced IL-12p40 expression in IFN-gamma/TLR-stimulated macrophages in an IRF-8-dependent manner contributing to the elicitation of innate immune in macrophages (70). Delalleu et al., analysing salivary proteome biomarker profiles from patients with pSS, demonstrated that macrophage related proteins represented one of the biomarker signatures of pSS (71). There are few data on the polarisation of macrophages in patients with pSS. In the study from Aota et al., there was an inverse correlation between the number of CXCR3⁺ CD163⁺ macrophages and the lymphocytic infiltration suggesting that CXCR3⁺CD163⁺M2 macrophages may contribute to the anti-inflammatory functions in pSS lesions (72). Myeloid-derived suppressor cells (MDSC) are a heterogeneous group of immature myeloid cells with immunosuppressive functions, playing different roles in autoimmune disorders including systemic lupus erythematosus and rheumatoid arthritis (115). In mice with ESS, a critical involvement of GITR/GITRL pathway in MDSCs was reported during disease development (116). The suppressive capabilities of MDSCs gradually decreased during ESS development, which was associated with the increased GITRL expression. Notably, blocking GITR signal in MDSCs restored their suppressive functions in ESS mice, suggesting that targeting GITR/GITRL axis in MDSCs might be a potential therapeutic strategy for treating pSS patients. A group of tissue-resident macrophages were detected in SG tissues from NFS/sld mice underwent neonatal thymectomy, a murine model for pSS (117). CD11bhi macrophages in SG produced a large amount of CCL22 which promoted T cell migration and IFNγ production (117). Moreover, administration of anti-CCL22 antibody markedly attenuated SG tissue inflammation (117).

**T cells**

Compelling evidence indicates that activated T cells drive pSS disease development by producing pro-inflammatory cytokines and regulating B cell functions. CD4⁺ T helper (Th) cells represent the majority (>75%) of the lymphocytes infiltrating the SG in pSS patients, especially in the mild lesions and/or at an early phase of the disease (73, 74). Genetic studies have revealed the association between MHC class II alleles and pSS susceptibility, highlighting the importance of the presentation of autoantigens to T cells and thus emphasising the role of T cells in the pathogenesis of the disease (75).

**Th1, Th2, Tfh cells**

Th1 cells are thought to play a major role in pSS, being the most relevant CD4⁺ cell population infiltrating inflamed SG (76). Increased Th1-related cytokine levels have been detected, at mRNA and protein levels, in SG of pSS patients (77, 78) and a prevalent type 2 IFN signature has been also related to a higher focus score (FS) (79). IFN-γ promotes the activation of epithelial cells by inducing inflammation, Fas-mediated apoptosis and finally leading to tissue damage (80, 81). In mice, the deletion of IFN-γ or IFN-γ receptor blocks the onset of pSS (82), whereas the overexpression of IL-12, a potent IFN-γ activator, is related to the development of pSS (83, 84). Moreover, the repeated Ro60 peptide immunisation resulted in SG dysfunction through the induction of Th1 cell immune response (85). Th2 cytokines levels were also found closely related to SG lymphocytic infiltration, were notably increased in SG with GC and/or severe B cell infiltrate (86) and, furthermore, IL-4 expression was detected in pSS complicated by B cell lymphoma (87, 88).

More recently, a highly specialised CD4⁺CXCR5⁺ memory Th cells population, named T-follicular helper (Tfh) cells, has been characterised as primarily involved in GC formation, B cells differentiation and maturation of high-affinity antibodies (89). These cells represent the major source of IL-21 (90), a cytokine abundantly expressed in pSS patients and associated with higher IgG1 levels, anti-Ro/SSA antibody titres and degree of lymphocytic infiltration (91). Circulating and SG Tfh cells are significantly expanded in pSS patients and their frequencies positively correlate with the autoantibodies titres, disease severity, B cells hyperactivity and plasma cells frequencies (92, 93). A decrease of circulating Tfh cells has been reported after treatment with Rituximab and it has been associated with the improvement of disease activity parameters (94).

CD4Cre Bcl6fl/fl mice with Tfh deficiency exhibited almost no lymphocytic infiltration in SG tissue and dramatically reduced autoantibodies upon ESS induction (129). Consistently, abnormal Ascl2-regulated Tfh responses were detected in NFS/sld mice with pSS-like phenotypes (130). In contrast, deletion of Bcl6 in Foxp3⁺ Treg cells resulted in defects of T follicular regulatory (Tfr) cells, which consequently led to elevated GC reaction and exacerbated ESS disease manifestations, suggesting a protective role of Tfr cells in pSS pathogenesis (129). Recent studies further revealed that Tfh responses were
restrained by IL-10-producing regulatory B cells during ESS development. Adoptive transfer of IL-10-producing B cells suppressed Th response and ameliorated disease symptoms in ESS mice (131), suggesting an interaction between B and T cells during pSS disease progression.

**Th17 cells**

Th17 cells also represent critical players in pSS pathogenesis. Clinical observations have suggested an involvement of IL-17 in pSS pathogenesis while results from animal models further demonstrated a pathogenic role of IL-17 as well as Th17 cells in pSS disease pathology. Notably, mice with IL-17 deficiency were resistant to ESS induction whereas adoptive transfer of Th17 cells restored disease phenotypes in these mice (119). Furthermore, proteasome inhibition by bortezomib treatment suppressed Th17 cell generation and ameliorated disease progression in ESS mice (120). Consistently, ablation of IL-17 restored normal saliva secretion and reduced glandular lympoctic infiltration in C57BL/6.NOD-Aec1Aec2 mice, a spontaneous model for pSS (121). IL-17 signalling plays a critical role in SG tissue pathology because IL-17 receptor blockade in SG attenuated disease pathology in these mice (122). In another model of pSS, Rag-1 deficient mice with transfer of M3R deficient splenocytes exhibited pSS-like symptoms associated with Th17 cell infiltration in SG (123). Accordingly, administration of a small molecule antagonist of RORγt, the master transcription factor of Th17 cells, ameliorated SG tissue inflammation in these mice (124). In pSS patients, increased RORγt/Th17 cell frequencies and IL-17 levels have been described in SG (16, 95, 96), where the activated Th17 cells contribute to acinar damage through the release of metalloproteinase 9 (MMP-9) by epithelial cells stimulated (97, 98). Higher IL-17 levels have been detected in saliva, tears and sera of pSS patients compared to HC or non-Sjögren’s sicca syndrome patients (96, 99-101) and they also positively correlate with the presence of GC and the titres of anti-Ro/SSA and/or anti-La/SSB (102). Besides IL-17, Th17 cells promote local and systemic inflammation by releasing IL-22 (103). Our group demonstrated a higher expression of IL-22 in pSS patients SG compared to patients with non-specific chronic sialoadenitis, furthermore identifying Th17 and NKp44+ cells as the main sources of this cytokine in pSS patients (104). Additionally, in a pSS animal model, Barone et al. reported that the increased secretion of IL-22 determines the ectopic expression of the lymphoid chemokines CXCL13 and CXCL12, respectively, by fibroblasts and epithelial cells, thus promoting B cell recruitment and GC formation (105).

**Treg and TRM cells**

Treg cells are regarded as the role of T-regulatory (Treg) cells in pSS is still few and controversial. Some studies reported decreased CD4+CD25+high cells levels in SG and circulating of pSS patients (106-108), whereas, in striking contrast, other research groups described higher or equal circulating Treg levels in pSS patients (109) and a positive correlation between Treg frequencies in SG and glands inflammation grade (110, 111). In an interesting study, authors reported the expansion of CD8+CD69+ CD103+ tissue-resident memory T (TRM) cells in pSS SG of both humans and mice, furthermore demonstrating that the depletion of CD8+ T cells protected mice from pSS development (112).

**Conclusions and perspectives**

Research over the past three decades has gone beyond phenomenology to establish an important role for the B cell in the aetiology and pathogenesis of SS. But despite the well established role of B cells, recently studies have focused on the complex pathogenetic mechanism occurring in pSS where more actors interplay to induce an aberrant immune response. It seems that resident glandular epithelial cells, innate lymphoid cells, T cells undergo activation in response to environmental triggers and activated T cells with different phenotype may contribute to the disruption of the glands also providing a stimulus for B cell activation.

**Take home messages**

- Primary Sjögren’s syndrome is characterised by infiltration of the exocrine glands and systemic B cell hyperactivation.
- Despite an ever-increasing focus on B cells that are critically involved in Sjögren’s syndrome pathogenesis, other cells are thought to play important roles.
- Although these populations have previously been underestimated, it is now clear that the stromal and epithelial cells, the cells of the innate immune response and T cells contribute to the development and persistence of inflammation in Sjögren’s syndrome.

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