REVIEW

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Out of the shadow of interleukin-17A: the role of interleukin-17F and other interleukin-17 family cytokines in spondyloarthritis

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Purpose of review
The last decade has witnessed tremendous advances in revealing an important role for the interleukin (IL)-17 cytokine family in the pathogenesis of spondyloarthritis (SpA). Although most attention has been focused on IL-17A, a potential role of other IL-17 family members in inflammation and tissue remodelling is emerging. Herein, I review recent studies covering the role of IL-17B-F cytokines in the pathogenesis of SpA.

Recent findings
Several recent studies provided new insights into the cellular source, regulation and function of IL-17F. IL-17F/IL-17A expression ratio is higher in psoriatic skin compared to SpA synovitis. IL-17F-expressing T cells produce different proinflammatory mediators than IL-17A-expressing cells, and IL-17F and IL-17A signal through different receptor complex. Dual IL-17A and IL-17F neutralization resulted in greater suppression of downstream inflammatory and tissue remodelling responses. Furthermore, there is additional evidence of IL-23-independent IL-17 production. In contrast to IL-17A, IL-17F and IL-17C, which play proinflammatory roles in skin and joint inflammation, an anti-inflammatory function is proposed for IL-17D. An increase in IL-17E is associated with subclinical gut microbiome alterations after anti-IL-17A therapy in SpA patients.

Summary
IL-17 family cytokines may act as agonists or antagonists to IL-17A contributing in concert to local inflammatory responses. Understanding their function and identifying their cellular sources, and molecular mechanisms driving their expression will be the key to designing rational therapies in SpA.

Keywords
interleukin-17C, interleukin-17D, interleukin-17E, interleukin-17F, interleukin-17 family cytokines, spondyloarthritis

INTRODUCTION

Strong evidence from clinical trials firmly placed interleukin 17A (IL-17A) in the centre of the pathogenesis of the spondyloarthritides (SpA), the group of related but phenotypically heterogeneous conditions that share common genetic and pathogenetic features [1–6]. Responders to anti-IL-17A therapy included naïve patients and those who did not respond to previous treatments [7–10]. Importantly, emerging evidence indicates that targeting IL-17A slows down structural damage (including bone erosions and pathological new bone formation) as IL-17A blockade inhibits radiographic disease progression in both, psoriatic arthritis (PsA) [6,11] and ankylosing spondylitis (AS) [12]. In addition, recent data suggest that IL-17A inhibition improves enthesitis in patients with PsA [13] and AS [14].

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KEY POINTS

- Innate cells, including MAIT, γδ T cells and ILC3s do not require IL-23 for IL-17F and IL-17A production.
- IL-17F-expressing and IL-17A-expressing T cells are differentially regulated and produce different pro-inflammatory mediators.
- A dominant IL-17F signature has been observed in PsO skin compared with a stronger IL-17A signature in SpA synovium.
- Preclinical data support the concept that dual blockade of IL-17A and IL-17F is required for optimal inhibition of downstream inflammatory and tissue remodelling responses.
- Clinical trials of dual IL-17A and IL-17F inhibition indicate high efficacy in PsO, PsA and AS.
- Head-to-head studies of bimekizumab and anti-IL-17A treatment are required to further evaluate whether targeting of both, IL-17A and IL-17F cytokines is superior to inhibition of IL-17A alone.
- The IL-17 family cytokines may act complementary or antagonistic to IL-17A contributing to the local inflammatory responses in SpA.

As to the related extra-articular manifestations, anti-IL-17A therapy demonstrated impressive clinical efficacy in treating skin psoriasis (PsO) [3,15,16], but was not effective in treating colitis [17] or uveitis [18]. In contrast, unexpectedly, blocking IL-23, the cytokine upstream of IL-17A was not effective in AS [19,20] though anti-IL-23 therapy did improve colitis [21,22]. Overall, the IL-17 axis holds great promise for the development of further disease-modifying therapeutic opportunities in SpA. However, the inability of IL-17A blockers to cover the entire disease spectrum and to achieve a major clinical response and sustained remission underscores the importance of the identification of additional drivers of the pathologic immune responses, tissue-specific pathways, and hierarchies. The list of attractive candidates comprises other IL-17 family members: IL-17B, IL-17C, IL-17D, IL-17E and IL-17F [23–25]. These structurally related to IL-17A yet less well-characterized cytokines could play complementary or antagonistic roles, hence may affect IL-17A-driven tissue inflammation and/or remodelling, contributing to the pathology of SpA. This review highlights the most recent studies featuring the role of IL-17B-F cytokines in SpA.

INTERLEUKIN-17F

Among the IL-17 family members, IL-17F shares the highest homology (55%) with IL-17A. Both cytokines can exist as disulphide-linked homodimers or as IL-17A/IL-17F heterodimers [26]. It was postulated that IL-17F is co-produced with IL-17A by Th17 cells under the control of STAT3 and RORgt transcription factors [27] and signals via the same heterodimeric receptor consisting of IL-17RC and IL-17RA. Similar to IL-17A, although to a lesser extent, IL-17F can synergize with other pro-inflammatory molecules, particularly with tumor necrosis factor alpha, but also with IL-1β, interferon (IFN)-γ and lipopolysaccharide, amplifying its inflammatory potential [28]. Therefore, a similar, albeit less potent pro-inflammatory function has been proposed for IL-17F in driving pathogenic responses. Recent studies have provided new insights into the cellular source, regulation and function of IL-17F.

Interleukin-23-independent production of interleukin-17A and interleukin-17F

Cole and colleagues [29▪▪] present important novel insight into the biology of IL-17A-producing and IL-17F-producing innate cells. They demonstrated that IL-17F is the dominant isoform produced by *in vitro*-stimulated mucosal-associated invariant T (MAIT) cells, a unique population of innate-like T cells with restricted T cell receptor (TCR) diversity that can function through both TCR-dependent and -independent pathways [30,31]. IL-17A-producing MAIT cells were identified in PsO skin [32] and PsA and AS joint [33–35], and their potential role in SpA pathogenesis is emerging [36,37]. Importantly, Cole *et al.* showed that MAIT cells can produce IL-17F (and IL-17A) in an IL-23-independent fashion, in response to TCR triggering combined with IL-12 and IL-18 cytokines stimulation *in vitro* [29▪▪]. In addition, ILC3s and γδ T cells were also capable of an IL-23-independent IL-17A and IL-17F production [29▪▪], supporting recent evidence that human entheseal γδ T cells can produce IL-17A without IL-23 receptor expression [38]. These data prompt the notion that IL-23-independent IL-17A and IL-17F production is a feature shared among innate lymphocyte family members [29▪▪]. Remarkably, the cytokine milieu that tunes the IL-17A and IL-17F production seems to be cell-type dependent. In contrast to MAIT and γδ T cells, which were dependent on IL-12 for IL-23-independent IL-17A and IL-17F production, ILC3s did not require IL-12 or IL-23 and produced IL-17A and IL-17F upon stimulation with IL-1β, IL-2 and IL-7 [29▪▪]. The ability of T cells and innate(-like) lymphocytes to produce IL-17A in response to cytokines other than canonical IL-23, in particular to IL-7 and IL-9 [34,39,40], has been demonstrated before [41–43]. Such IL-12-IL-23-independent IL-17A and IL-17F production by these, presumably (but not yet

proven) pathogenic cellular subsets could explain why targeting p19 subunit that is unique to IL-23, or p40 subunit common to both, IL-12 and IL-23, were not efficacious in AS [19,20]. As to the peripheral disease, our recent study investigating cellular and molecular changes in the PsA joint in response to IL-12/IL-23 blockade with ustekinumab revealed that although ustekinumab suppressed synovial inflammation through modulation of key pathogenic pathways, expression of IL-17A and IL-17F remained unaffected [44], supporting IL-23-independent IL-17A and IL-17F production in PsA joint. Whether it has a pathogenetic significance has to be assessed in head-to-head clinical trials of IL-17A or IL-17A-IL-17F versus IL-23 antagonists. Yet, a recent retrospective study in PsA demonstrated that treatment with secukinumab has a greater persistence rate than the treatment with ustekinumab [45]. Taken together, the emergence of distinct pathways culminating in the secretion of IL-17A and IL-17F cytokines, in addition to the canonical IL-23/IL-17A pathway, underscores the importance of the IL-17A/IL-17F axis in the pathogenesis of SpA, provides insights into understanding results of clinical trials and urges to identify pathogenic cell populations in target tissues.

Distinct regulation and function of interleukin-17F

Recent findings challenged the notion that IL-17F has a redundant role in SpA pathogenesis. In the study of Cole *et al.*, only a minor population of MAIT cells produced IL-17A upon *in vitro* stimulation despite uniform expression of RORgt. Instead, MAIT cells as well as ILC3s and γδ T cells produced predominantly IL-17F [29▪▪], supporting the concept that IL-17A and IL-17F are differentially regulated [46,47]. High expression of IL-17F can be also induced in canonical CD4+ T cells [48▪▪], but in contrast to innate lymphocytes, this process is dependent on IL-23. In this study, Burns *et al.* identified and characterized three CD4+ T cell subsets: IL-17A+IL-17F-, IL-17A+IL-17F+, and IL-17A-IL-17F+. Interestingly, these populations displayed different cytokine profiles: while all subsets contained similarly high frequencies of cells expressing TNF, IL-17A-IL-17F+ cells expressed less IL-10 and GM-CSF and more IFN-γ compared to IL-17A+IL-17F- CD4+ T cells [48▪▪]. Based on previous molecular characterization of IL-10-expressing Th17 subsets [49], the authors proposed that IL-17F-expressing CD4+ T cells might represent the 'pathogenic' subtype, although in-depth molecular and functional characterization of these cells is required to conclude about their pathogenicity. Notably, IL-17F and IL-17A-expressing T cells differ not only in their molecular profiles but also are differentially regulated. Comparing the induction of CD4+ T cells by LPS-activated monocytes versus soluble anti-CD28 mAb and L-1β and IL-23 stimulation, Burns and colleagues observed that while both stimuli induced IL-17A+IL-17F+ CD4+ T cells, only the latter resulted in IL-17F+IL-17A- CD4+ T cells [48▪▪]. Further analysis revealed that IL-17F expression in CD4+ T cells is driven by high-strength TCR stimulation in the presence of IL-23 and IL-1β. IL-17F induction is partially mediated via IL-2-dependent mechanism, as IL-2 blockade significantly reduced the CD28-mediated increase in frequencies of IL-17F+ CD4+ T cells [48▪▪], in line with previous findings showing that high levels of IL-2 shift the balance between IL-17A and IL-17F towards IL-17F production by murine T cells *in vitro* [50]. Interestingly, another study in mice demonstrated that the activation of transmembrane TNF (tmTNF)-TNF Receptor 2 signalling stimulates IL-2 expression and regulates IL-2 mRNA stability [51]. Given a marked increase of tmTNF in SpA synovitis and its impact on key pathological features of SpA [52] along with the observation that IL-17F levels are strikingly higher than IL-17A in the blood of patients with SpA [53] it might be revealing to examine tmTNF-IL-17F axis in SpA. Importantly, reports by Cole *et al.* and Burns *et al.* demonstrate that IL-17F is not only differentially regulated but also significantly contributes to inflammation, as dual IL-17A and IL-17F blockade were more effective at reducing IL-17-driven pro-inflammatory responses by human dermal fibroblasts [29▪▪] and synovial fibroblasts [48▪▪] compared to blockade of IL-17A alone, according to previous findings [54] (Fig. 1). Attempting to detect IL-17F-expressing cells *ex vivo*, Cole *et al.* confirmed the presence of single-positive for IL-17A or IL-17F, as well as double-positive MAIT cells in psoriatic lesional skin [29▪▪] (Fig. 1). In contrast, Burns *et al.* failed to detect the presence of IL-17F-expressing cells in PsA synovial fluid directly *ex vivo*, although confirmed the potential of synovial fluid mononuclear cells to produce IL-17F upon *in vitro* stimulation [48▪▪]. Could be these discrepancies explained by tissue-specific expression of IL-17F? Previous findings demonstrated that IL-17F levels are approximately 30-fold higher than IL-17A levels in PsO skin [53]. Our recent study using paired biopsies of skin and synovium collected from PsA patients with active PsO confirmed a higher IL-17F to IL-17A ratio in the inflamed skin and revealed that the relative expression of IL-17A versus IL-17F is inversed in inflamed joint and skin compartments with IL-17A being more than 30-fold higher than IL-17F in the joint [55▪] (Fig. 1). Taken together these *in vitro* and *ex vivo*

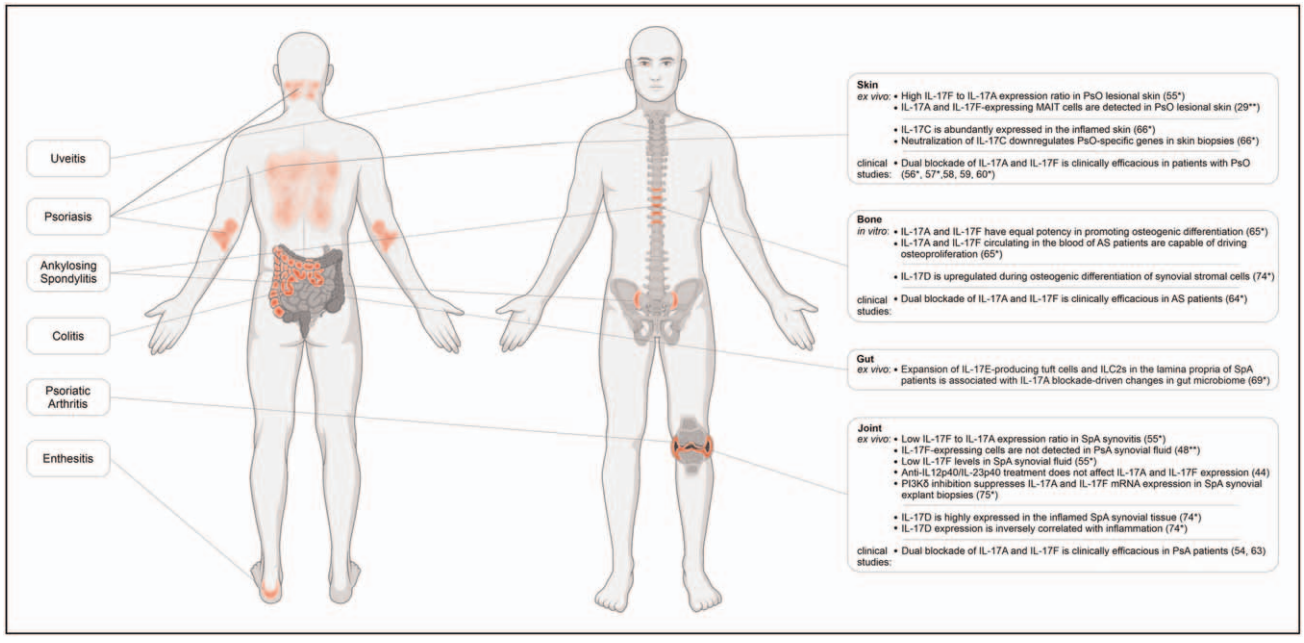

FIGURE 1. Recent *ex vivo, in vitro and in vivo* evidence supporting the role of IL-17 family cytokines in the pathogenesis of SpA. Created with BioRender.com. SpA, spondyloarthritis.

data point towards a nonredundant role for IL-17F and provide new pathobiological insights in joint versus skin inflammation, suggesting that (1) the contribution of IL-17F to chronic tissue inflammation may be more prominent in the skin than in joint; (2) IL-17F has the potential to contribute to pathology, therefore dual blockade of IL-17A and IL-17F can further reduce inflammation.

The preclinical data supporting the efficacy of the dual IL-17A and IL-17F blockade is further underpinned by recent clinical-trials evidence for bimekizumab, a humanized monoclonal IgG1 antagonist neutralizing both cytokines [54]. Two recent Phase 3 studies reported the safety and efficacy of bimekizumab for the treatment of moderate to severe plaque PsO [56▪,57▪] confirming phase 2 findings [58,59] and revealing the superiority of dual IL-17A and IL-17F targeting to the targeting of IL-12/IL-23 in achieving complete skin clearance. Similarly, simultaneous inhibition of IL-17A and IL-17F in patients with PsO was more effective than inhibition of TNF in terms of the speed, depth and durability of skin clearance [60▪]. Superior efficacy of IL-17A blockade relative to inhibition of IL-12/IL-23[61] and TNF [62] in clearing skin PsO has been demonstrated previously. Ongoing head-to-head comparator study of bimekizumab and anti-IL-17A treatment (BE RADIANT, http://clinicaltrials.gov/ct/show/NCT03536884) will provide important knowledge on whether targeting of both cytokines is clinically more beneficial than inhibition of IL-17A alone. Bimekizumab is also effective in treating peripheral and axial SpA. It has been first assessed in the proof-of-concept study [54] and strengthened in followed up phase 2b study that patients with PsA, who were administered bimekizumab, showed marked and sustained improvements in their condition compared with placebo [63]. Also, for an axial disease, a phase 2b study revealed a rapid onset and greater ASAS40 response rates as well as sustained improvements across secondary outcomes of disease activity for bimekizumab versus placebo [64▪].

Role in bone pathology

Another recent study employing an *in vitro* model of osteogenic differentiation of human periosteal cells puts forward the argument that IL-17F does not only contribute to IL-17A but has equal potency in promoting osteogenic differentiation, in contrast to its less potent role in driving inflammatory responses [65▪] (Fig. 1). IL-17A and IL-17F cytokines, circulating in the blood of AS patients, are also functionally active as they were capable of driving osteoproliferation *in vitro* [65▪] (Fig. 1). Accordingly, neutralization of both cytokines by bimekizumab resulted in greater suppression of γδ or Th17 T-cell supernatants-mediated, or AS patient's serum-mediated *in vitro* bone formation than the blockade of IL-17A or IL-17F individually [65▪]. These results provide further scientific evidence to validate the clinical relevance of the dual IL-17A and IL-17F blockade in patients with AS for preventing or suppressing pathological periosteal bone formation.

OTHER MEMBERS OF THE INTERLEUKIN-17 FAMILY

A very limited number of recent studies address the role of other IL-17 family members in SpA. Lauffer *et al.* demonstrated that IL-17C, a member of the IL-17 family that, in contrast to IL-17A and IL-17F, is mainly produced by epithelial cells and keratinocytes, is broadly expressed in the inflamed skin of patients with various inflammatory skin diseases including but not limited to PsO [66▪]. The study revealed that IL-17C establishes a self-amplifying circuit in synergy with TNF, leading to the secretion of pro-inflammatory cytokines by keratinocytes and the recruitment of immune cells to the site of inflammation (Fig. 1). Using human disease models, Lauffer *et al.* demonstrated significant downregulation of PsO-specific genes after neutralization of IL-17C, considering IL-17C as a promising drug target for the treatment of inflammatory skin diseases [66▪]. However, since IL-17C is regulated by IL-17A and TNF, as both therapies rapidly reduce IL-17C expression in PsO skin [67,68], the added-value of the developing of IL-17C-specific therapy in SpA needs to be further established.

Another recent study suggests an association between IL-17A blockade-driven changes in the gut microbiome of SpA patients and the expansion of IL-17E-producing tuft cells and ILC2s in the lamina propria [69▪]. Whether IL-17E drives gut inflammation after IL-17A inhibition remains to be assessed. IL-17E has been shown to promote PsO [70], however, its role in gut inflammation is confusing as it has been demonstrated to induce colitis [71,72] or to protect against colitis [73].

IL-17D is the least investigated member of the IL-17 family. Our recent data on the cellular source and function of IL-17D suggest its unique position among other IL-17 family cytokines [74▪]. First, IL-17D is abundantly expressed in inflamed SpA joint, higher than other IL-17 cytokines. Second, IL-17D is expressed by stromal cells, in particular, by cells similar to multipotent mesenchymal stromal cells. Third, IL-17D expression inversely correlates with inflammation (Fig. 1). Furthermore, IL-17D is upregulated during osteogenic differentiation of synovial stromal cells *in vitro*. However, *in vitro* functional assays in bone precursor cells and *in vivo* experiments in *IL-17d–/–* mice failed to demonstrate a critical role for IL-17D in bone homeostasis. Instead, *IL-17d–/–* mice were more prone to arthritis development than littermate controls and presented with enhanced systemic inflammation at the peak of serum-transfer arthritis [74▪]. Based on these data it is tempting to propose that IL-17D exerts an anti-inflammatory effect on synovial cells, yet further research is required to address its role in the pathogenesis of SpA.

DIRECTIONS FOR FUTURE RESEARCH

Further investigations of the exact mechanisms of production and function of IL-17 family members will provide novel insights into their roles in SpA pathogenesis and may have direct relevance for the targeted therapy. Could we imagine other ways to target IL-17A and IL-17F production? Recently we demonstrated that PI3Kδ inhibition dampens both IL-17A and IL-17F expression in innate-like lymphocytes and Th17 cells in IL-23-independent and the dependent manner *in vitro* as well as in primary cells derived from blood and synovial fluid of SpA patients [75▪]. This inhibition has functional anti-inflammatory and anti-remodelling effects on target cells, such as synovial fibroblasts. Furthermore, we demonstrated that the PI3K-Akt-mTOR pathway is active in the SpA joint and PI3Kδ inhibition suppresses IL-17A and IL-17F expression in SpA synovial explant biopsies *ex vivo* [75▪]. In light of the results from in vitro models, simultaneous suppression of IL-17A and IL-17F is a promising direction in IL-17-mediated diseases, however, more data is needed to conclude about its added value on clinical response over IL-17A inhibition. Moreover, accumulating evidence suggests that IL-17A and IL-17F may exert distinct, even opposite downstream activities, which may impact the clinical outcome. For instance, IL-17A-blockade is ineffective for Crohn's disease [17]. It was concluded, that IL-17A is important for maintaining barrier integrity and has a protective role in colitis [76]. However recent data may suggest an alternative explanation. First, the IL-17F pathway has been demonstrated to promote inflammation in the intestines through its effect on the intestinal microbiome. Consequently, IL-17F neutralization suppressed the development of colitis whereas blocking of IL-17A did not [77]. Second, a recent mechanistic study revealed that IL-17A inhibits the expression of IL17-lineage cytokines through a negative feedback loop. Accordingly, the loss of IL-17A in Th17 cells did not reduce their pathogenicity, resulting in the elevated expression of GM-CSF and IL-17F cytokines [78]. Third, recent findings demonstrated that in contrast to IL-17A homodimers or IL-17A/IL-17F heterodimers that signal via heterodimeric IL-17RA/IL-17RC receptor, IL-17F preferentially associates with IL-17RC homodimers, leading to IL-17RA-independent signalling [79▪]. Given that it is plausible to propose that aggravation of Crohn's pathology by IL-17A neutralization could be not due to a decrease

in IL-17A but rather due to upregulation of IL-17F and increased signalling via IL-17RC/IL-17F axis. In this context, it is perhaps not surprising that anti-IL-17RA treatment with brodalumab resulted in worsening Crohn's disease [80].

CONCLUSION

Accumulating evidence suggests that IL-17 family members have tissue-specific functions in inflammation. Their differential cellular sources, expression levels and function in different target tissues could contribute to tissue-discrete results for IL-17 axis inhibition across the SpA spectrum. Additionally, there is evidence for interaction between IL-17 cytokines, including self-reinforcing, feed-forward as well as negative feedback mechanisms leading to agonistic or antagonistic effects on tissue inflammation and/or remodelling. Therefore understanding the function of IL-17 family cytokines, as well as detailed characterization of cellular subsets and molecular mechanisms culminating in their expression, will be the key to designing rational therapies in SpA.

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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This work demonstrated that innate lymphocytes, including MAIT cells, gd T cells and ILC3s produce predominantly IL-17F cytokine and identified IL-17F-producing cells in psoriatic lesional skin. The authors extended a previous finding that dual blockade of IL-17A and IL-17F is required for optimal inhibition of downstream inflammatory responses. Furthermore, this study provides further evidence towards the contribution of IL-17A and IL-17F to tissue inflammation independently of IL-23, advancing our understanding of divergent results of therapeutic targeting IL-17A and IL-23 in AS.

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