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Brief Reviews

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IL-21–Producing Th Cells in Immunity and Autoimmunity

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IL-21 is a member of the common γ-chain signaling family of cytokines. Analyses of the behavior of immune cells in response to IL-21 in vitro and studies of mice deficient in IL-21 or its receptor indicate that IL-21 has a role in lymphocyte activation, proliferation, differentiation, and survival. IL-21–producing CD4$^+$ Th cells constitute a broad array of helper subtypes including T follicular helper cells and Th17 cells. Both autocrine and paracrine utilization of IL-21 contributes to the overall signal transduction pathways of the Ag receptor to influence the growth and survival of lymphocytes. The redundancy that IL-21 exhibits in lymphoid organs during immune responses is in stark contrast to the evidence that pharmacological neutralization of this cytokine can halt inflammation in nonlymphoid organs where IL-21 becomes the dominant voice. *The Journal of Immunology*, **2013, 191: 3501–3506.**

Interleukin-21 is an IL-2 family cytokine produced by activated T cells to regulate immune responses (1). This pleiotropic cytokine functions in both an autocrine and paracrine manner (2) via a heterodimeric receptor consisting of the specific IL-21R and the common γ-chain receptor, with the latter also being shared by IL-2, IL-4, IL-7, and IL-15. Other cells such as NKT cells and γδ T cells have also been reported to produce IL-21 (1, 3). Importantly, IL-21 is pivotal to Th cell differentiation (2, 4–8) as well as driving the expansion and promoting the survival of both CD4$^+$ and CD8$^+$ T cells (1, 9, 10). CD8$^+$ T cells are an important target of the actions of IL-21. Transgenic overexpression of murine IL-21 revealed predominant expansion of memory phenotype CD8$^+$ T cells (11), and numerous studies have demonstrated that CTL functions are also dependent on IL-21 (1, 12). In addition to T cells, B cells rely on IL-21 for survival and differentiation, supporting the production of Ab-forming cells with class-switched Ig (13). Although IL-21 has important lymphocyte-intrinsic effects, IL-21R is widely expressed on cells of both the adaptive and innate immune system as well as nonimmune cells (14, 15).

IL-21 is strongly linked with inflammation and autoimmunity. We previously reported that increased levels of IL-21 mRNA and IL-21–dependent increases in T cell expansion formed a basis for autoimmunity in the NOD mouse (9). Elevated amounts of IL-21 have subsequently been reported in many autoimmune diseases, including type 1 diabetes (T1D) (9, 14, 16), systemic lupus erythematosus (SLE) (17, 18), and inflammatory bowel diseases (IBDs) (19, 20), where IL-21 protein and mRNA levels were correlated with disease severity. These findings are likely to reflect the fact that activated T cells, which are enriched during inflammation, produce IL-21. IL-21 as a product of acute inflammation is highlighted by the observation that the amounts of IL-21 in peripheral blood and mucosa of IBD patients in remission are not significantly different from those of healthy individuals (19, 21). The contributing role of IL-21 to autoimmunity has been confirmed in several studies showing that mice were protected from autoimmune diseases including T1D (22–25), lupus (26), colitis (20), and rheumatoid arthritis (RA) (27) when IL-21 signaling is blocked, or in mice genetically deficient in IL-21 or IL-21R.

IL-21 drives inflammation by promoting the expansion and survival of lymphocytes. Studies also show that IL-21 can inhibit the induction of Foxp3$^+$ regulatory T (Treg) cells (2, 4). However, whether IL-21 acts directly upon Treg cells or makes effector cells less "suppressible" remains controversial. Apart from priming the immune system, IL-21 has also been reported to have inhibitory effects via the induction of subsets of IL-10–producing Treg and B cells. The IL-12 cytokine family member IL-27, as well as IL-6, induces IL-10–producing Foxp3$^-$ regulatory type 1 T cells in an IL-21–dependent manner; these Treg cells coproduce IL-21 (28, 29).

Whereas IL-21 can be produced by many CD4$^+$ T cells, specific helper subsets have been reported to secrete IL-21 at the highest levels, namely T follicular helper (Tfh) cells (30), Th17 cells (2, 4, 5, 30), and recently described CCR9-bearing Th cells in mucosal tissues (10). In this review we discuss these Th cell subsets and their roles in immunity and autoimmunity.

Tfh cells. Tfh cells are a specialized subset of CD4$^+$ T cells that provide help to B cells for the generation of Ab-forming cells that produce affinity-matured Ab (31). Tfh cells, as their name suggests, are localized within B cell follicles. Tfh cells migrate into specialized structures formed inside B cell follicles known as the germinal center (GC) through high surface expression CXCR5 and downregulation of CCR7 that guides Tfh cells

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Abbreviations used in this article: EAE, experimental autoimmune encephalomyelitis; eYFP, enhanced yellow fluorescent protein; GC, germinal center; IBD, inflammatory bowel disease; PD-1, programmed cell death 1; PP, Peyer's patches; RA, rheumatoid arthritis; ROR, retinoic acid–related orphan receptor; SLE, systemic lupus erythematosus; T1D, type 1 diabetes; Tfh, T follicular helper; Treg, regulatory T.

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away from the T cell zone where the ligands for CCR7 (CCL19 and CCL21) are expressed and toward the ligand for CXCR5 (CXCL13), a chemoattractant produced by follicular dendritic cells at the central locus of the GC (32, 33). Tfh cells are typically characterized by high expression of both CXCR5 and the coinhibitory molecule programmed cell death 1 (PD-1). Tfh cells are selectively derived from precursors with high affinity to Ag (34), consistent with the observation that the magnitude of Tfh cell generation is influenced by costimulation of the TCR (6) and by Ag dose delivered at initial contact with dendritic cells (35). However, Tfh cells reciprocally depend on B cells; whereas the initial differentiation of Tfh cells can be mediated by APCs, such as dendritic cells, in the absence of B cells (35), the maintenance and function of this subset during GC reactions is B cell–dependent (36).

In addition to CXCR5 and PD-1, Tfh cells are characterized by high expression of cell surface molecules and cytokines that are important for the interaction with B cells (i.e., CD40L, ICOS, IL-4, and IL-21) (31). Tfh cells have been reported to produce the highest amounts of IL-21, a cytokine that is also important for their differentiation and survival (2, 6, 8, 37). IL-21 has been well established to support the generation and differentiation of B cells (17, 38). For Tfh cell generation or differentiation, IL-6 exhibits redundancy with IL-21 (39, 40) and furthermore promotes IL-21 production during T cell activation (5, 8). However, to what relative extent both cytokines are used by Tfh cells during an immune response in unmanipulated mice or in humans remains unknown. The extent to which responsiveness to IL-21 is required for Tfh cells during the generation of Ab responses remains controversial. This may be due to the influence of costimulation by IL-21 being dependent on the form of Ag delivered, variations of whether a functional readout for Tfh cells (affinity-matured Ab) was used in studies, which has been confounded by a phenotypic characterization of Tfh cells that is based on surface markers that are commonly expressed on activated $CD4^+$ T cells. A recent study has highlighted this issue, demonstrating that despite being phenotypically "Tfh-like," IL-21R–deficient Tfh cells were functionally devoid of B helper activity and that IL-21 signaling was intrinsically required in $CD4^+$ T cells to generate fully functional Tfh cells for the generation of long-term humoral immunity to viruses (41). Whether IL-21 influences Tfh cells in a quantitative or qualitative manner remains an important unanswered question.

The transcription factor Bcl-6 is necessary for Tfh cell generation (42). IL-21 influences the expression of Bcl-6, *Prdm1* (encoding Blimp-1) (17, 43), and c-Maf (44), transcription factors that are central to Tfh development. Expression of IL-21 and c-Maf are mutually dependent, as c-Maf is reported to transactivate IL-21, and accordingly IL-21 expression is deficient in c-$Maf^{-/-}$ mice (29, 44). Consistent with the important role of STAT3 signaling cytokines such as IL-21 and IL-6 for Tfh cells, STAT3 deficiency compromises the generation of human Tfh cells (45). IL-27, in turn, induces IL-21 production by T cells in a STAT3-dependent manner and is required for Tfh cell function as well as GC responses (46). Whereas IL-27 is necessary for optimal Tfh cell generation, it is not sufficient to drive this program. In addition to inducing IL-21, IL-27 induces IL-21R expression (29) and enhances expression of pivotal Tfh molecules, including ICOS and c-Maf, and promotes survival of Tfh cells (29, 46). In contrast to Th17 cells, TGF-β is not required for Tfh cell differentiation (8). In fact, exogenous TGF-β has been shown to inhibit IL-21 secretion induced by either IL-6 or IL-21 (47).

Although Tfh cells, at the population level, are characterized by high production of IL-21, expression of this cytokine is not essential for their effector functions at the individual cell level. After immunization, only a fraction (30–40%) of Tfh cells secreted IL-21 throughout different phases of the response (30). Indeed, $IL\text{-}21^-$ Tfh cells were reported to function just as well as $IL\text{-}21^+$ Tfh cells, including localization to the B cell follicles, expression of CXCR5 and PD-1, providing help to B cells, and inducing class switching (30). Tfh cells are reported to secrete effector cytokines other than IL-21, including IL-4 and IFN-γ (48). However, the extent to which Tfh cells secrete other cytokines has been the subject of controversy, which could reflect experimental variations in their induction and differentiation (6, 8, 44, 49).

Th17 cells. IL-17–producing $CD4^+$ T cells feature prominently in inflamed tissues and have been implicated in both protective and pathogenic functions in the immune system. In addition to their hallmark cytokine IL-17 (IL-17A), Th17 cells also produce IL-17F, IL-21, and IL-22 (50). In mice, TGF-β is required for the induction of both proinflammatory Th17 and peripherally induced Treg cells (50). TGF-β and IL-6 coordinately induce Th17 cell differentiation, whereby IL-6 is a switch factor that promotes Th17 cell development while inhibiting the induction of Treg cells (50). Initially, IL-23 was identified as the differentiation factor for Th17 cells from naive T cells, but it was subsequently demonstrated to be a cytokine critically required for the stabilization of existing Th17 cells (51, 52) and to enhance the pathogenicity of Th17 cells (53, 54).

IL-21 is produced by Th17 cells, and the primary roles for IL-21 in mouse Th17 cell development are expansion of existing Th17 cells (52) and antagonizing induction of Treg cells in the periphery (2, 4). However, Th17 cells can develop in the absence of IL-21/IL-21R signaling (55, 56). Similar to Tfh cells, IL-6 induces the production of IL-21 in Th17 cells, and in turn IL-21 induces expression of IL-23R on Th17 cells, thus further stabilizing the phenotype (5). Indeed, generation of Th17 cells is reported to be impaired in the absence of IL-21 signaling (2, 4, 5). $IL\text{-}21^{-/-}$ T cells display suboptimal Th17 cell generation in vitro, demonstrating the ability of IL-21 to act in an autocrine manner for Th17 cell differentiation.

Transcription factors cruicial for Th17 development include retinoic acid–related orphan receptor (ROR)γt, STAT3, and IFN regulatory factor 4. RORγt, encoded by *Rorc*, has been considered the master regulator of Th17 cells, whereas IRF4 is essential for IL-21 signaling (57–59). STAT3 is required for signaling of several cytokines critical to Th17 cell development and function, including IL-6, IL-21, IL-23, and IL-22 (2, 5, 60). Defective Th17 responses have been reported in mice deficient in any of these transcription factors. In line with these observations, immunodeficient patients with dominant-negative mutations in *STAT3* are profoundly deficient in circulating Th17 cells (61–63).

$CCR9^+$ Th cells. Recently, we described a subset of IL-21–producing Th cells that expressed the gut-homing receptor CCR9 (10). $CCR9^+$ Th cells from the pancreas and pancreatic

draining lymph node of NOD mice that spontaneously develop T1D did not produce cytokines associated with Th1, Th2, or Th17 or express *Gata3* or *Rorc* mRNA. However, they did express Tfh cell–associated molecules, including ICOS, Bcl-6, and c-Maf, and supported production of Abs by B cells. Analogous to Tfh cells, CCR9$^+$ Th cells are expanded in the peripheral blood of patients with Sjörgren's syndrome and in autoimmune mice. Intriguingly, these Tfh-like cells did not express CXCR5 (10). However, CCR9$^+$ Th cells that coexpressed CXCR5 (CCR9$^+$ Tfh cells) were also identified in NOD mice (10). Interestingly, CCR9$^+$ Tfh cells in the Peyer's patches (PP) upregulated prototypical Th17 molecules, including *Il17a*, *Il17f*, *Rorc*, *Il22*, *Il23r*, and *Ccr6* (C. King, unpublished observations). It is plausible that these cells represent Tfh cells activated in the tissues associated with mucosal inflammation, thereby acquiring CCR9 expression (Fig. 1). Indeed, effector T cells have been demonstrated to convert to a Tfh cell–like phenotype in the PP to induce IgA production (64), and this is discussed in more detail below.

Plasticity of Th cells and the relationship between IL-21–producing Th cells. The molecular pathways that govern Tfh and Th17 cell differentiation substantially overlap, and functional similarities exist between them (49, 65, 66). The differentiation of both of these Th subsets can be induced by IL-6 and IL-21, and they rely on STAT3 signaling for their development (2, 5, 45, 61). Expression of c-Maf is also common (44), and costimulation via ICOS/ICOSL interactions is critically required for the development of both helper subsets (6, 44, 67). Furthermore, in autoimmune BDX2 mice, IL-17 from CD4$^+$ T cells promotes the formation of GC and is pivotal to the unrestrained production of autoantibodies via direct effects on B cells (49).

One of the initial hints that Th17 cells retained plasticity came from the observation that Th17 cells converted to an IFN-γ–producing phenotype after adoptive transfer, even when IL-17–producing cells were highly purified using specific tetramers (68, 69). By using more sophisticated tools and methods for tracking T cells in vivo, it became apparent that endogenous Th17 cells could transform into Th1, Tfh, or Treg cells or retain a Th17 phenotype, depending on the nature of the immune response and the microenvironment of the target tissue (64, 70, 71). Using fate-reporter mice, in which cells that produced IL-17 at any point during their development permanently switched on enhanced yellow fluorescent protein (eYFP) expression, Th17 cells could be seen to transition from IL-17$^+$IFN-γ$^-$ to IL-17$^+$IFN-γ$^+$ and again to IL-17$^-$IFN-γ$^+$ expression (71). This study also confirmed that the switch of Th17 cells to IFN-γ production was necessary for the development of experimental autoimmune encephalomyelitis (EAE) and showed that this process was facilitated by IL-23. Such fate-mapping experiments validated the previous conclusion drawn that conversion of adoptively transferred Th17 cells to IFN-γ production was a requirement for the development of T1D in NOD mice (69).

Suppressive Th17 cells that produce IL-10 were discovered in the small intestine using IL-17A-eGFP reporter mice (70), similar to those identified in in vitro experiments (53). Under noninflammatory conditions, CCR6-expressing Th17 cells preferentially home to the intestinal mucosa where the expression of its ligand CCL20 is enriched. At this site, Th17 cells could be converted either to a regulatory phenotype (70) or a Tfh cell–like phenotype in the PP (64). A follow-up study using fate-reporter mice showed that Th17 cells downregulated *Il17a* and *Rorc* and transitioned into Tfh cells in the PP. In fact, Tfh cells in the PP that help B cells make Ag-specific IgA were absent in Th17-deficient mice (64). Under steady-state conditions, almost half of the Tfh cells in the PP of mice were former Th17 cells (eYFP$^+$), and of these ex-Th17 cells, up to 20% switched to a Tfh cell phenotype expressing CXCR5, PD-1, *Il21*, and *Bcl6* (64). Upon immunization with cholera toxin, the proportion of eYFP$^+$ cells that converted to

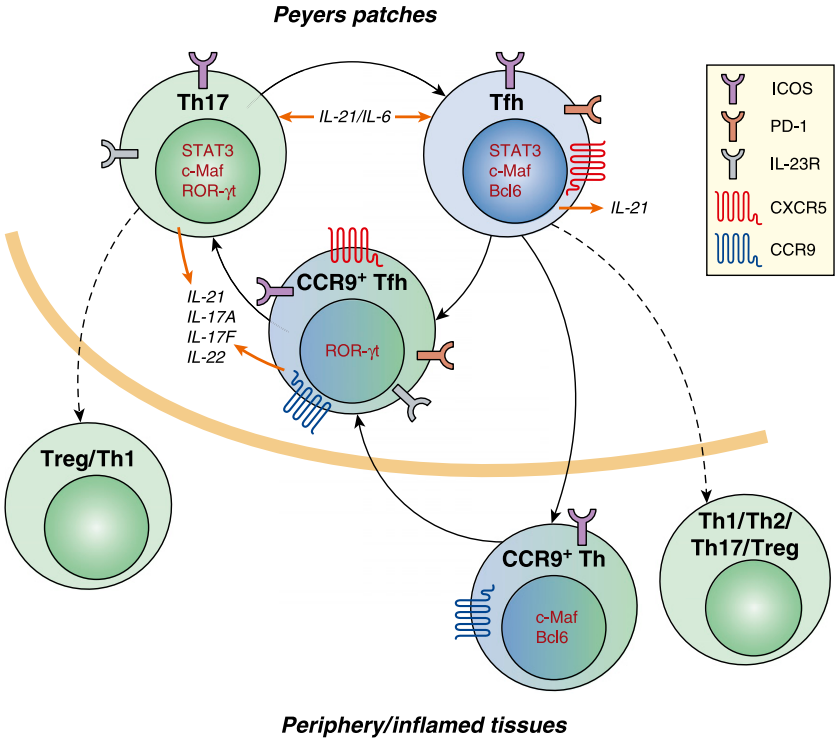

FIGURE 1. Transitioning between sequential Th programs. Plasticity of IL-21–producing Th cells in gastric mucosal tissues and accessory organs is shown. Dotted lines indicate potential for conversion to other Th cells in different inflamed tissues and microenvironments. The solid black arrows represent conversion from one Th program to another in the gut microenvironment.

a Tfh cell phenotype increased and was associated with strong Ag-specific IgA production. The mechanism of the transition from Th17 to Tfh cells in the PP remains unclear.

Tfh cells can initiate secondary programs as functional Th1/Th2/Th17/Treg cells depending on local environmental cues (72). Upon adoptive transfer, IL-21$^+$ Tfh cells from IL-21 reporter mice had the potential to differentiate into conventional effector cells (30). Tfh cells have been reported to acquire effector functions associated with other Th subsets, producing IL-17 (44, 49), IL-4 (48), and IFN-γ in some studies, but not IL-17 (6, 8) or IL-4 (48) in others. Foxp3$^+$ Treg cells have been demonstrated to transform into Tfh cells in the PP upon adoptive transfer (73). Recent studies have proposed that Tfh cells are controlled by Foxp3$^+$ follicular Treg cells, which are a specialized subset of Tfh cells that colocalize within B cell follicles and exhibit characteristics attributed to both Tfh cells and Treg cells, but lack expression of CD40L, IL-4, and IL-21 (74). Abrogating either follicular Treg cell development or their follicular localization was shown to enhance GC responses (74–76).

Th cells were well established as a Th1/Th2 paradigm almost two decades ago. In the new millennium, IL-17–producing Th cells were identified as a subset distinct from Th1 and Th2, and the generation of these cells was shown to be mutually antagonistic with Foxp3$^+$ Treg cells (77–79). With the excitement generated by this discovery, new reports amassed rapidly of other Th subsets that selectively produce IL-22 (Th22) (80) and IL-9 (Th9) (81, 82) as well as other regulatory subsets (regulatory type 1 T cells, Th3) (28, 83, 84). During this time, Tfh cells were also reported to be a distinct lineage (8). However, the understanding of Th cell differentiation has shifted toward a view that acknowledges the flexibility of Th cell phenotypes as well as the cooperation of different T cell subsets during an immune response (Fig. 1).

IL-21–producing Th cells in autoimmunity. One mechanism by which IL-21 drives autoimmunity is by expanding and promoting the survival of pathogenic T cell subsets in nonlymphoid tissue. Our previous work showed that autoimmune-susceptible mice produce more IL-21 compared with autoimmune-resistant strains (9, 16) and that IL-21–producing T cells increased with progression of autoimmunity (10). Furthermore, we showed that the requirement for IL-21 for islet inflammation was continuous to sustain the inflammation (25). Blockade of IL-21 led to a significant reduction in the inflammatory infiltrates into the islets, and islet graft rejection mediated by CD8 T cells was found to be IL-21–dependent (25). Similarly, *Il21r*$^{-/-}$ NOD mice fail to develop insulitis and are protected from T1D (22–24). Further supporting a role for IL-21 in driving autoimmunity, diabetes could be induced by overexpression of IL-21 in the islets, even on a diabetes-resistant background (24). We recently reported that NOD mice deficient in IL-21 signaling exhibit a Treg cell/Th17 ratio skewed in favor of Treg cells (14). This observation is in line with IL-21 promoting Th17 cells while concomitantly inhibiting the induction of Treg cells (2, 4).

IL-21 can also act on parenchymal cells to promote inflammation. For example, colonic myofibroblasts and epithelial cells respond to IL-21 by secreting matrix metalloproteases as well as producing chemokines to recruit other inflammatory cells in IBD (85). In the gut mucosa, IL-21–producing Th cells are elevated in Crohn's disease and ulcerative colitis. Although IL-21–producing Th cells coexpressing CXCR5 as well as IL-17 were identified, most were found to coproduce IFN-γ (86). IL-21$^+$ Tfh cells in mucosal tissues, but not blood, were observed to be higher in Crohn's disease compared with healthy controls (86). This study also showed an increase in Th17 cells in the lamina propria of IBD patients.

Excessive numbers of Tfh cells lead to autoimmunity, as evidenced in the *sanroque* mice carrying a mutation in the *Roquin ubiquitin ligase* gene (87). Roquin was identified as a negative regulator of ICOS and Tfh cells. This mutation causes an increased accumulation of Tfh cells and elevated autoantibody production that manifest as an SLE-like disease. Indeed, it has been reported that Tfh cells are required for development of Ab-mediated autoimmunity (88). BXSB mice carrying a *Yaa* mutation develop severe SLE; however, IL-21R–deficient BXSB-*Yaa* mice do not develop autoimmunity and lack characteristic features, including spontaneous GC formation, hypergammaglobulinemia, and kidney pathology (18). CCR9$^+$ IL-21–producing Th cells are also associated with autoimmune disorders (10). This subset is enriched in blood and accessory organs of the gastrointestinal tract of mice prone to autoimmunity, namely in the pancreas, pancreatic draining lymph node, PP, and salivary gland. In patients with Sjögren's syndrome, we reported elevated frequencies of CCR9$^+$ Th cells in the peripheral blood (10).

The first evidence that Th17 cells, rather than Th1 cells, were the key drivers of autoimmunity in the CNS stemmed from studies using an EAE mouse model (51). Since then, Th17 cells have been found to be critically important in autoimmune disorders targeting other organs; mice with a Th17 defect owing to deficiencies in mediators that promote, or are produced by, Th17 cells were protected against many autoimmune diseases, including EAE, RA, and T1D (4, 14, 22–24, 68, 69, 89, 90). Therefore, Th17-targeted therapies have been developed and under clinical trials, including anti–IL-17A mAbs for the treatment of autoimmune diseases such as psoriasis and RA (91).

The capacity for IL-21 to influence the survival and differentiation of both T cells and B cells makes it an attractive target for therapeutic intervention in a wide range of inflammatory diseases. Antagonizing IL-21 in conjunction with islet transplantation is a promising strategy to treat T1D. Blockade of IL-21 halts inflammatory destruction of insulin-producing β cells and prevents islet graft rejection; the combined treatment allowed the mice to regain endogenous β cell function (25). Antagonizing the function of IL-21 is also a promising therapy for IBD, as this has been reported to reduce disease development (21).

Conclusions

IL-21 is a pleiotropic cytokine produced at different stages and immunological sites of an immune response. The requirements for IL-21 production and the generation of Th cells that produce it are disease- and tissue-specific. Emerging data describing the plasticity of Th cells are helping us reconcile and explain the conclusions drawn from earlier studies. During a specific Th program, IL-21–producing T cells can express patterns of markers, cytokines, and transcription factors functionally specific for a particular response, and concomitantly express molecules that are antagonistic to other programs, conserving the ability to take cues from changing microenvironmental factors during the course of an immune response.

Disclosures

The authors have no financial conflicts of interest.

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