Novel epigenetic therapy for Th17 cell mediated autoimmune inflammatory diseases

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Immunopathogenesis leads to autoimmune and inflammatory diseases of many organs with variable clinical manifestations. The eye can be seriously affected. A common ocular autoimmune complication, autoimmune uveitis, can lead to irreversible blindness. Currently the first line treatment for autoimmune uveitis is corticosteroids.1 However, some patients do not respond to steroids. Some steroid treated patients may develop systemic and ocular side effects such as osteoporosis, cataract and glaucoma.2 The use of biologics is an alternative treatment for these patients to replace steroids, but the complicated nature of the pathogenesis in uveitis hampers the effectiveness of these alternative agents.3 New targets for biologics development are still in desperate need.

CD4+ T helper (Th) cells play a crucial role in autoimmunity by eliciting adaptive immune responses. Various Th cell lineages exhibit specific host defense responses against specific pathogenic factors by various polarizing mechanisms that are precisely regulated by cytokines and epigenetic machinery including histone modifications, DNA methylation, nucleosome remodeling and chromatin organization.4 Previously DNA methyltransferase inhibitor, Zebularine and bromodomain, and extra-terminal (BET) protein inhibitor, OTX015 have been reported to suppress the Th17 cell mediated autoimmune uveitis in experimental animal models.5,6 Although these drugs show undesirable systemic toxicity with suboptimal specificity, they indicate the clinical applicability of epigenetics as a novel treatment for autoimmune uveitis.7,8

In a recent issue of eBioMedicine, Hu et al. proposed a new epigenetic treatment for autoimmune uveitis.9 The team identified five potential candidates from a pool of 128 epigenetic inhibitors that suppress expression of IFN-γ in Th1 cells and IL-17 in Th17 cells in the experimental animal model of autoimmune uveitis, without compromising cell viability. IOX1, an inhibitor of 2-oxoglutarate (2OG)-dependent oxygenases, could alleviate immunologic responses, because of its preferential inhibition of Th17 cells. RNA-Seq analysis and qPCR revealed that upstream transcription factors of Th17 differentiation were not affected by IOX1 treatment. Conversely, suppression of the Th17 downstream signature cytokines Il17a and Ccl20 expression was observed, indicating a direct regulatory role of IOX1 on Th17 differentiation. IOX1 was found directly interacting with the TET2 DNA demethylase via cellular thermal shift assays and biolayer interferometry. Bisulfite sequencing, chromatin immunoprecipitation, and chemical-immunoprecipitation showed direct binding of IOX1 to the CpG-6-8 site in the Il17a promoter that led to less demethylated DNA on these sites. The adoption of TET2 deficient CD4+ T cells further validated the inhibitory ability of IOX1 towards Th17 polarization and IL-17 and CCL20 expression.

To study the effects of the IOX1 and Th17 interaction in vivo, the anti-inflammatory efficacy of IOX1 was investigated in an experimental autoimmune uveitis (EAU) animal model. IOX1 treated EAU mice showed less severe clinical symptoms than the solvent control treated group. Furthermore, flow cytometry analysis indicated systemic administration of IOX1 can significantly reduce intraocular pro-inflammatory T cell populations but not affect the systemic T cell counterparts.

This elegant study depicted an epigenetic mechanism involving Th17 cells with a newly found molecular target of IOX1 which suppresses Il17a expression by directly targeting TET2 activity on its promoter in Th17 cells. This refined molecular mechanism can help development of epigenetic therapy for inflammatory diseases. The eye, in particular, is a therapeutic site since it is susceptible to T-cell mediated immune responses and prone to develop autoimmune uveitis due to circulating retinal antigen-specific T cells to cognate antigens.9,10 Treatment with IOX1 in EAU animals could reduce the migration/infiltration of Th17 cells into the site of inflammation and tissue damage. In addition to Th17 cells, this study also revealed some interesting observations on other types of immune cells. The in vitro drug screening in this study indeed showed that IOX1 could dramatically inhibit Th1 cells. However, a similar inhibition was not observed in the in vitro polarized Th1 cells. Therefore, it is worth investigating this intriguing discrepancy. Can IOX1 also regulate Th1 cells via TET2? How IOX1 affects Th17 physical cell migration, as

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suggested by the reduction in CCL20 expression has to be explored. Another critical migration marker CCR6 could also be quantified in the eye-infiltrating Th17 cells. Also, the cell migration process can be further verified by tracing the corresponding antigen-specific T cells. Such investigations will contribute to better understanding of the all-rounded effects of IOX1 on effector cells in autoimmune uveitis and other autoimmune inflammatory diseases.

Contributors
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Declaration of interests
The authors declare no conflict of interest.

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