Th1/Tc1 polarized tissue resident memory T cells mediate checkpoint blockade–induced dermatitis and colitis via IFNγ and TNFα

Robin Reschke[1]
Jason W Shapiro[2], Sherin J Rouhani[3], Daniel J Olson[3], Yuanyuan Zha[4] and Thomas F Gajewski[5]
[1] University of Chicago, Pathology , 60615 Chicago, USA
[2] University of Chicago, Center for Research Informatics, 60615 Chicago, USA
[3] University of Chicago, Medicine, Section of Hematology/Oncology, 60615 Chicago, USA
[4] University of Chicago, Human Immunological Monitoring Facility, 60615 Chicago, USA
[5] University of Chicago, The Ben May Department for Cancer Research , 60615 Chicago, USA

Background & objectives

Immune checkpoint blockade (ICB) has been immensely successful in treating a variety of

cancers including melanoma or cutaneous squamous cell carcinoma. Off-target effects of ICB are called

immune-related adverse events (irAE). IrAEs can cause inflammation of all organ systems but most

frequently affect the skin or gastrointestinal tract. To prevent treatment pauses or cessation it is

detrimental to investigate the immunopathology of irAEs.

Methods

We used a variety of modern spatial techniques consisting of multiparameter immunofluorescence, RNA in situ

hybridization (RISH), and spatial transcriptomics on FFPE tissue of irAE dermatitis (22 cases) and irAE colitis (8 cases). IrAE

dermatitis was compared to psoriasis (3 cases) and healthy skin samples (10 cases). IrAE colitis was compared to healthy

colon samples (8 cases).

Results

Multiparameter IF could show an expansion of CD4+ and CD8+ tissue-resident memory T (TRM)

cells in the lymphocytic infiltrate of the skin in cutaneous irAEs compared to healthy skin controls. Spots

containing TRM cells were then analyzed with spatial transcriptomics to explore the functional phenotype

of TRMs. Expression of Th1-associated genes was upregulated in irAE. Downstream IFNγ induced genes

such as HLA-DRA, CD74, and GBP5 as well as chemokine (CXCL9/10/11) were upregulated as well.

As expected, *Th17- asociated genes were found to be more expressed in psoriasis cases.*

In addition, increased expression of inhibitory checkpoints such as PD-1, CTLA-4, LAG-3, TIM-3 and

TIGIT was observed in irAE cases. IF in concert with RISH technology confirmed the expression

of IFNγ, TNFα, CXCL9, and CXCL10 within CD45+ cells in irAE dermatitis and irAE colitis. Looking more closely,

we found that IFNγ transcripts were found specifically within TRM cells. The Th1-centered phenotype

was also observed in irAE colitis cases compared to healthy colon and ulcerative colitis.

Conclusion

TRM cells with upregulated inhibitory checkpoints are likely re-activated by ICB. The Th1/Tc1-

based immune response with increased production of IFNγ and TNFα argues that severe steroid-refractory

irAE dermatitis could potentially be targeted with systemic TNFα-blockade and topical JAK inhibitors could

be considered for low-grade irAE dermatitis as corticosteroid sparing reagents.