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Editorial

Hero or villain? The heterogeneity of Th17 cells

The story of Th17 cells started in 2005, when a new type of T helper cells with IL-17-producing ability was discovered (Harrington et al., 2005; Park et al., 2005). Since then, Th17 cells have emerged as a major player and fundamentally involved in infectious, inflammatory, and autoimmune diseases and cancer. The in vivo functions of Th17 cells are context-dependent and are perplexing, as they can be protective or destructive during health and disease conditions. The inherent complexity of Th17 cells may due to the fact that these cells are heterogeneous.

The concept "pathogenic/non-pathogenic Th17" was proposed as an important deviation in the past decade to appreciate the dichotomy of Th17 cells during diseases. Although relevant to diseases, some of them can be very destructive while others may remain harmless. In this special issue, Schmidt et al. tackle the machinery of IL-17 signaling in renal diseases. Specifically, they focus on glomerulonephritis, a leading cause for end-stage renal disease. They suggest that anti-Th17/IL-17 cytokine treatment has the potential to become a promising therapeutic strategy for glomerulonephritis patients. Zheng et al. discuss the cellular source and the role of IL-17 signaling during Type 1 diabetes (T1D) progression. They re-analyze previously published transcriptomics data and demonstrate that islets may directly receive IL-17 signal. They also explore the influential role for IL-17 affecting distal tissues during diabetic complications. These analyses provide insights into the IL-17-based T1D treatment. There are also many other inflammation-related diseases that are tightly related to IL-17. For example, acute myocardial infarction (AMI), a leading cause of morbidity and mortality, involves IL-17-mediated pathogenesis. In this special issue, Mora-Ruíz et al. specifically discuss the effector function of IL-17 on cardiomyocytes, smooth muscle cells and immune cells during AMI. In many inflammatory and autoimmune diseases, researchers find that a subset of Th17 cells producing both IL-17 and IFN-γ is more pathogenic. On some occasions, these cells are known as "Th1-like Th17 cells". These cells express Th17 lineage-specific transcription factor RORγt, as well as Th1 lineage-specific transcription factor T-bet. Kamali et al. highlight the pivotal role of these cells in autoimmune disorders. They summarize clinical reports associated with increased Th1-like Th17 cells. Specifically, they discuss the mechanism of how Th17 cells are transdifferentiated into Th1-like Th17 cells. This review exhibits that the plasticity is critically important for the generation of pathogenic Th17 cells during autoimmunity.

One reason for the diversified pathogenicity of Th17 population is the cytokine regimen. IL-6 and TGF-β1 are commonly recognized cytokines to induce Th17 generation (Bettelli et al., 2006; Mangan et al., 2006; Veldhoen et al., 2006; Manel et al., 2008; Volpe et al., 2008). Disruption of SKI/SMAD4 complex licenses this IL-6-induced Th17 generation (Zhang et al., 2017). Moreover, other cytokines, e.g. IL-21, IL-1β, IL-23, TGF-β3 and activin, or cytokine combinations are also proved to be essential for both the differentiation and pathogenicity of Th17 cells. In this special issue, Zhang et al. address the mechanism of IL-21-induced Th17 differentiation. Given the fact that IL-6-induced Th17 can be profoundly impaired by the deficiency of IL-21 signaling (Korn et al., 2007; Nurieva et al., 2007; Zhou et al., 2007), this research article further reinforces the SKI/SMAD4 serving as a universal switch for TGF-β signaling-promoted Th17 generation. Although TGF-β signaling is vital for the differentiation and pathogenicity of Th17 thorough multiple mechanisms (Zhang, 2018), there is always an exception. A combination of IL-6, IL-1β, and IL-23 can generate pathogenic Th17 cells in the absence of TGF-β signaling (Ghoreschi et al., 2010). This regimen is frequently used as a standard in vitro pathogenic Th17 culture condition, yet it is still unclear whether it represents a homogeneous or heterogeneous Th17 population.

The heterogeneity of Th17 cells is orchestrated not only by cytokine regimen but also by many environmental cues, such as diet, microbiota, pollutants, and even circadian rhythm. These different factors can precisely regulate cellular signaling network and result in highly heterogeneous Th17 cell population. Luckily, the contemporary technology confers opportunities to elaborate the complications. Single-cell RNA sequencing provides needed tools to delineate the transcriptomic profiles of individual cells. Gaublomme et al. first used this technology to identify novel regulators that control pathogenicity without affecting the differentiation of Th17 cells. Among the spectacular datasets, they successfully identified GRP65, TOSO, PLZP and CD5L as major switches controlling pathogenicity (Gaublomme et al., 2015). This tool is powerful to discover markers and transcription factors that are relevant to pathological process. Recently, Karmaus et al. applied single-cell RNA sequencing and defined two Th17 subsets in an autoimmune disease model, stemness Th17 and plastic Th1-like Th17, selectively expressing transcription factor TCF-1 and T-bet, and discretely expressing CD27 (Karmaus et al., 2019). These results confirm that Th17 cells are not only phenotypically and transcriptionally heterogeneous, but also metabolically heterogeneous via mTORC1 as a central regulator for fate decision. In this special issue, Shi et al. summarize the studies related to the network of Th17 cells metabolism, and highlight a new era for the research of Th17.

Th17 cells link adaptive immune response with innate immunity. As the first line of defense, the innate immunity can facilitate adaptive immune response by inflammasome activation and the production of proinflammatory cytokine IL-1β and IL-18. Recently, NLRC3, a non-inflammasome-forming member of the NLR innate immune receptor family, was reported to be essential in regulating Th17 differentiation (Uchimura et al., 2018). Deng et al. systematically summarize the inflammasome activation and Th17 responses, and emphasize the importance of IL-1 signaling in Th17-associated disorder. In addition to T cells, emerging evidence show innate or innate-like immune cells are

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also important source of IL-17, which include γδT cells, NKT cells, and Type 3 innate lymphoid cells (ILC3). Similarly, these cells are also highly heterogeneous. In this special issue, Chen et al. provide opinions about the complexity of liver γδT cells render either pro-inflammatory or anti-infection ability through regulation IFN-γ or IL-17 production. Interestingly, a most recently paper also mentioned TCF-1 as a key regulator that can be antagonized by c-Maf to promote the commitment of IL-17-producing γδT cells (Zuberbuehler et al., 2019). Tsagaratou unveils the transcriptional and epigenetic regulation mechanisms of NKT17. She also summarizes a list of phenotypes in mice with altered NKT17 development. This review therefore shed lights on the IL-17-producing subset of the heterogeneous iNKT population.

Given the heterogeneous nature of Th17, one would certainly not be surprised in the future if Th17 or IL-17-producing cells divided into more subsets. Recent studies continue adding fuel to the fire. Articles in this special issue provide insights and perspectives into the potentials of novel immunotherapies for a variety of Th17-related diseases.

References

Harrington, L.E., Hatton, R.D., Mangan, P.R., Turner, H., Murphy, T.L., Murphy, K.M., et al., 2005. Interleukin 17-producing CD4+ effector T cells develop via a lineage distinct from the T helper type 1 and 2 lineages. Nat. Immunol. 6, 1123–1132.

Park, H., Li, Z., Yang, X.O., Chang, S.H., Nurieva, R., Wang, Y.H., et al., 2005. A distinct lineage of CD4 T cells regulates tissue inflammation by producing interleukin 17. Nat. Immunol. 6, 1133–1141.

Bettelli, E., Carrier, Y., Gao, W., Korn, T., Strom, T.B., Oukka, M., et al., 2006. Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells. Nature 441, 235–238.

Mangan, P.R., Harrington, L.E., O'Quinn, D.B., Helms, W.S., Bullard, D.C., Elson, C.O., et al., 2006. Transforming growth factor-beta induces development of the T(H)17 lineage. Nature 441, 231–234.

Veldhoen, M., Hocking, R.J., Atkins, C.J., Locksley, R.M., Stockinger, B., 2006. TGFbeta in the context of an inflammatory cytokine milieu supports de novo differentiation of IL-17-producing T cells. Immunity 24, 179–189.

Manel, N., Unutmaz, D., Littman, D.R., 2008. The differentiation of human T(H)-17 cells requires transforming growth factor-beta and induction of the nuclear receptor RORgammat. Nat. Immunol. 9, 641–649.

Volpe, E., Servant, N., Zollinger, R., Bogiatzi, S.I., Hupe, P., Barillot, E., et al., 2008. A critical function for transforming growth factor-beta, interleukin 23 and proinflammatory cytokines in driving and modulating human T(H)-17 responses. Nat. Immunol. 9, 650–657.

Zhang, S., Takaku, M., Zou, L., Gu, A.D., Chou, W.C., Zhang, G., et al., 2017. Reversing SKI-SMAD4-mediated suppression is essential for TH17 cell differentiation. Nature 551, 105–109.

Korn, T., Bettelli, E., Gao, W., Awasthi, A., Jager, A., Strom, T.B., et al., 2007. IL-21 initiates an alternative pathway to induce proinflammatory T(H)17 cells. Nature 448, 484–487.

Nurieva, R., Yang, X.O., Martinez, G., Zhang, Y., Panopoulos, A.D., Ma, L., et al., 2007. Essential autocrine regulation by IL-21 in the generation of inflammatory T cells. Nature 448, 480–483.

Zhou, L., Ivanov, I.I., Spolski, R., Min, R., Shenderov, K., Egawa, T., et al., 2007. IL-6 programs T(H)-17 cell differentiation by promoting sequential engagement of the IL-21 and IL-23 pathways. Nat. Immunol. 8, 967–974.

Zhang, S., 2018. The role of transforming growth factor beta in T helper 17 differentiation. Immunology 155, 24–35.

Ghoreschi, K., Laurence, A., Yang, X.P., Tato, C.M., McGeachy, M.J., Konkel, J.E., et al., 2010. Generation of pathogenic T(H)17 cells in the absence of TGF-beta signalling. Nature 467, 967–971.

Gaublomme, J.T., Yosef, N., Lee, Y., Gertner, R.S., Yang, L.V., Wu, C., et al., 2015. Single-cell genomics unveils critical regulators of Th17 cell pathogenicity. Cell 163, 1400–1412.

Karmaus, P.W.F., Chen, X., Lim, S.A., Herrada, A.A., Nguyen, T.M., Xu, B., et al., 2019. Metabolic heterogeneity underlies reciprocal fates of TH17 cell stemness and plasticity. Nature 565, 101–105.

Uchimura, T., Oyama, Y., Deng, M., Guo, H., Wilson, J.E., Rampanelli, E., et al., 2018. The innate immune sensor NLRC3 acts as a rheostat that fine-tunes t cell responses in infection and autoimmunity. Immunity 49, 1049–1061 e6.

Zuberbuehler, M.K., Parker, M.E., Wheaton, J.D., Espinosa, J.R., Salzler, H.R., Park, E., et al., 2019. The transcription factor c-Maf is essential for the commitment of IL-17-producing gammadelta T cells. Nat. Immunol. 20, 73–85.

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