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INSIGHTS

Stand by me(mory): Chronic infection diminishes memory pool via IL-6/STAT1

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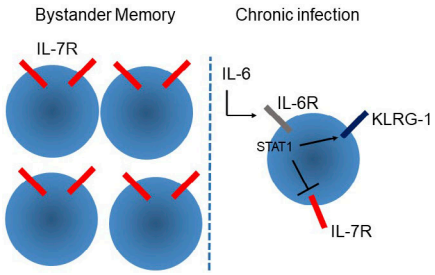
Despite great efforts to eradicate chronic viral infections, they still remain a global health problem. In this issue, Barnstorf et al. (2019. *J. Exp. Med.* https://doi.org/10.1084/jem.20181589) show that virus-unspecific bystander memory T cells are highly affected during chronic viral infection via IL-6/STAT1. Bystander memory T cells are strongly decimated in numbers and change in phenotype and function during chronic viral infection. These data provide new explanations for immune-mediated problems during chronic virus infections.

In this issue of *JEM*, Barnstorf and colleagues describe the effect of chronic viral infections on heterologous bystander memory T cells. Chronic viral infection highly reduced bystander memory T cells and caused phenotypic and functional changes. The phenotypic changes were dependent on IL-6 and STAT1 during chronic viral infection (see figure). Accordingly, following chronic viral infection, bystander memory T cells showed limited secondary expansion and reduced control during antigen rechallenge (Barnstorf et al., 2019).

Chronic viral infections still remain a global health problem, with millions of people affected worldwide. Accordingly, these findings on heterologous memory bystander T cells are highly relevant because chronic infections may change number, phenotype, and function of memory T cells. In fact, vaccination of patients suffering from chronic viral infections can fail (Stelekati and Wherry, 2012). Consistently, memory T cell formation was impaired in mice chronically infected with the murine lymphocytic choriomeningitis virus (LCMV)



During chronic viral infection, bystander memory T cells change in phenotype number and function via IL-6/STAT1.

model system (Stelekati et al., 2014). Moreover, memory T cells face apoptosis and attrition during acute and chronic LCMV infection, with lasting depletion during chronic viral infection (McNally et al., 2001; Kim and Welsh, 2004). Interestingly, depletion correlated with the presence of type I IFNs (IFN-I), and prominent IFN-I inducers such as poly(I:C) likewise induced memory T cell depletion (McNally et al., 2001). Consistently, IFN-I receptor (IFNAR)–deficient mice did not exhibit reduction in memory T cell subsets (McNally et al., 2001; Stelekati et al., 2014). Furthermore, prolonged IFNAR signaling prevented transition of T cells from effector to memory (Stelekati et al., 2014).

Barnstorf et al. now show that bystander memory T cells change in number, phenotype, and function during chronic infection. Phenotypic changes such as expression of effector and exhausted T cell subsets were dependent on IL-6 and STAT1 (Barnstorf et al., 2019). While the data on STAT1 would be consistent with previous reports, blockade of the IFNAR did not change the phenotype of bystander memory T cells in these settings. Notably, the phenotypic changes of heterologous memory T cell immunity were rather affected by IL-6. IL-6–deficient mice exhibit late exhaustion of virus-specific T cells, which results in prolonged virus persistence (Harker et al., 2011). STAT3, which is activated downstream of the IL-6 receptor–gp130 complex, is itself critical for establishment of memory T cells (Cui et al., 2011; Ives et al., 2013). Furthermore, T cell–specific STAT3-deficient mice show reduced follicular T helper cells and limited antibody production and fail to

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control LCMV (Ray et al., 2014; McIlwain et al., 2015). IL-6 can induce phosphorylation of both STAT1 and STAT3 in resting T cells, while a reduction of STAT1 can be observed after T cell activation (Teague et al., 2000). Interestingly, Barnstorf et al. (2019) do not observe a difference in STAT3 phosphorylation, in sharp contrast to STAT1 phosphorylation, when bystander memory T cells were incubated with IL-6. The underlying mechanism remains unclear and could be investigated in future studies. Moreover, the role of classic vs. trans IL-6 signaling might differentially impact bystander memory T cells and could be examined in the future. The reduction of bystander memory T cells was partially dependent on perforin, which was rather associated with LCMV-specific T cells than with other perforin-producing cells important for regulating anti-viral T cell immunity such as natural killer cells (Crome et al., 2013). However, the reduction of bystander memory T cells, the impact of perforin, and/or LCMV-specific T cells in this context remain interesting research topics, since the reduction could be not rescued completely by perforin and other

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effects such as tissue damage likely influence the presence of bystander memory T cells and are also dependent on LCMV-specific T cells and perforin.

How could the findings of Barnstorf et al. (2019) be related to human disease? During chronic virus infections (i.e., HBV and HCV), autoimmune phenomena are well described (Piconese et al., 2018). Similarly, it is known that the failure rate of vaccinations is enhanced during chronic infection with HBV and HCV (Yao and Moorman, 2013). The findings of Barnstorf et al. (2019) could deliver an interesting explanation for these phenomena. However, more studies will be required to give specific insights. Besides direct immune-related problems, chronic viral replication promotes induction of cancer. In fact, chronic HIV, HBV, and HCV are all associated with enhanced incidence of different types of cancers. A beneficial role of anti-tumor $CD8^+$ T cells in the control of melanoma is well established (Larkin et al., 2015). One might speculate from the data of Barnstorf et al. (2019) that modulation of the anti-tumor memory T cell pools might contribute to enhanced cancer development during chronic viral infection.

In summary, Barnstorf et al. show a reduction of bystander memory T cells in number, phenotype, and function during chronic viral infection. Phenotypic changes were attributed to IL-6 and STAT1, and blockade of IL-6 could rescue function of bystander memory T cells during chronic infection. These findings might be highly relevant for vaccination in patients who acquire chronic infections.

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