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Letter to Editor Open Access

Role of USP 18 in Immune Response to Chronic Viral Infection

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Type I IFNs is vital for host defense against viral and bacterial infections. In addition, type I IFNs are also acknowledged to be involved in many immunoregulatory processes, such as NK cell activation [1] and proliferation/survival of CD8+ T cells [2,3]. Beside their well-known role in innate immunity, type I IFNs are constitutively expressed at a low level to ensure the maintenance of cellular homeostasis and may also play a role in shaping the adaptive immunity [4-6]. This constitutive IFN expression may, however, have detrimental effects if not tightly controlled. Usp18 is an IFN-inducible cysteine protease of the ubiquitin-specific protease family [7] and acts as an ISG15 deconjugating protease in the ISGylation system [8]. Furthermore, Usp18 functions in the type I IFN pathway by down regulating the JAK/STAT pathway independently of its isopeptidase activity through an interaction between Usp18 and the IFNAR2 subunit of the type I IFN receptor complex, whereas neither IFNAR1 nor IFNGR1 (type II IFN) receptor subunits were able to interact with Usp18 [9]. Usp18-deficient cells have enhanced IFN-a/b signaling and more ISG15 modified proteins [10]. As confirmed by gene expression microarray, the expression of IFN-inducible genes is increased and prolonged in the absence of Usp18 [8]. Accordingly, a deficiency in Usp18 increases the sensitivity of cells to IFN-I [9]. Consistently, Usp18-deficient mice exhibit limited viral replication after infection. How Usp18 expression influences the immune response, however, is still not completely understood. The amount of antigen presented is a crucial determinant of the adaptive immune response. *In vitro* studies found that only 10 peptide–MHC (pMHC) complexes can form an immunological synapse between DCs and T cells [10]. However, low-affinity T-cell receptors (TCRs) require a larger dose of antigen than high-affinity TCRs [11]. Henrickson et al. found that DCs require at least 2×10^4pMHC complexes to induce T-cell proliferation in lymph nodes *in vivo*. Additionally, the duration of the initial priming phase is inversely correlated with the amount of antigen presented [12].These findings suggest that a larger dose of antigen improves T-cell immunity. Consistently, low-dose application of inactivated virus results in limited induction of neutralizing antibodies, whereas replicating virus leads to a strong antibody response [13,14]. Accordingly, a specific compartment that promotes viral replication and increases the presented dose of antigen might improve the adaptive immune response.

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