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Tissue T cells in prophylactic and therapeutic vaccination responses

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ABSTRACT

In this conference report, I highlight the potential to target tissue-resident T cells to enhance prophylactic and therapeutic vaccine immunity. I describe our recent findings on exploiting frontline sentinal immunosurveillance by liver-resident immunity for functional cure of hepatitis B. We showed that therapeutic vaccine-induced HBV-specific T cells are constrained by liver-resident NK cells; cytokine-activation and PD-L1 blockade of NK cells converted them into helpers able to instead boost HBV-specific T cells. Turning to tissue-resident T cells in the lung, we found this pool can include T cells able to recognise SARS-CoV-2, including cross-reactive responses present prior to the pandemic. The importance of inducing T cells with future prophylactic vaccines was underscored by their selective expansion in a subset of donors aborting SARS-CoV-2 infection without detectable antibodies.

In this summary of my conference presentation at the Advances in Targeted Therapies Meeting 2023 I will discuss our recent research on roles for, and constraints on, tissue T cells in vaccine responses. I will briefly describe our work on enhancing the *liver T cell* response to *therapeutic* vaccination for hepatitis B (*HBV*) and move on to the rationale for targeting *airway T cells* in *prophylactic* vaccination for *SARS-CoV-2*. Our research focuses on tissue-resident memory T cells (T_{RM}) because these are increasingly recognised to be optimally adapted to their local niche and able to provide rapid and sustained frontline defence at the site of infection [1,2]. For example, we have identified a population of CD8+ T_{RM} whose progeny can survive more than a decade in human liver and are associated with HBV control [1].

HBV remains one of the leading causes of death worldwide, necessitating a concerted effort to develop novel antiviral and immunomodulatory approaches able to mediate sustained off-treatment responses (functional cure). Therapeutic vaccines are a compelling immunotherapeutic backbone because they are easily administered and should specifically boost T and B cells directed against HBV [3]. There is a new generation of therapeutic vaccines being tested, using highly immunogenic prime/boost constructs containing all the major HBV antigens. However, the efficacy of therapeutic vaccines has been limited by markedly attenuated T cell responses in the setting of chronic HBV infection, driven to exhaustion and deletion by decades of high antigen load. We have additionally defined immunosuppressive interactions with neighbouring cells in the tolerogenic liver microenvironment that constrain HBV-specific T cell responses [3]. For example, the liver is enriched for NK cells, that can act as potent rheostats, able to exert both positive and negative regulatory effects on antiviral T cells [3,4]. We therefore investigated whether manipulation of NK cells can alter the liver T cell response to therapeutic vaccination in HBV.

Using an adenoviral vector to deliver HBV to mouse hepatocytes and establish chronic infection, we tested the impact of NK cells on the T cell response to a therapeutic vaccine [5] (currently in Phase II trials in subjects with chronic hepatitis B). Depletion of NK cells prior to vaccine administration significantly boosted the frequency of functional HBV-specific T cells in this model. Further experiments confirmed that the negative regulation of therapeutic vaccine-induced HBV T cells was mediated by liver-resident NK cells. Probing tractable pathways of NK cell regulation identified constitutive expression of PD-L1 by liver-resident NK cells, that was further upregulated by HBV infection, accompanied by a concomitant striking upregulation of PD-1 on intrahepatic HBV-specific T cells. A functional role for the PD-1 pathway was supported by preferential rescue of PD-1^{hi} T cells by NK depletion, which phenocopied PD-1 blockade, and confirmed by showing that PD-1 knockout T cells were resistant to NK cell inhibition [5].

Such negative regulation of T cells by NK cells has been shown to be critical for tissue health, limiting responses to prevent the induction of autoimmunity during viral infection [6]. However, the other side of the coin is a detrimental effect on the efficient local expansion of antiviral T cells in response to therapeutic vaccination. We went on to demonstrate that cytokine activation and PD-L1 blockade could convert NK cells from negative to positive regulators, able to help the expansion of

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HBV-specific T cells in the mouse model and using PBMC from subjects with chronic HBV [5]. Cytokine activation of NK cells and PD-1 blockade are both approaches being trialled in the clinic in chronic viral infections and cancer that can be combined with therapeutic vaccination; we are exploring additional strategies to re-programme pathogenic interactions between liver-resident T and NK cells.

Tissue-resident T cell immunity is also well-recognised to be critical in the control of respiratory pathogens [2]; our recent findings support the harnessing of mucosal immunity to enhance the capacity of next generation SARS-CoV-2 vaccines to provide infection-blocking protection [7,8]. Through intensive monitoring of healthcare workers recruited to COVIDsortium early in the first UK wave, we identified a new outcome of exposure to SARS-CoV-2, which we termed 'abortive' infection [9]. A subset of individuals remained repeatedly negative on weekly PCR and antibody testing but expanded SARS-COV-2 T cells and had induction of an interferon-induced signal (IFI27); together these findings suggested that T cells had aborted subclinical infection without virus or antibodies becoming detectable [8]. Crucially, the individuals with abortive infection had T cell responses with differentially skewed SARS-CoV-2 specificities compared to those with classical seropositive infection. Pre-existing T cells able to cross-recognise SARS-CoV-2 were most frequently directed against the RNA polymerase (NSP12), the region we found to be most highly conserved across all variants and all *coronaviridae [8]*. This provides a rationale for targeting polymerase and other proteins of the replication transcription complex that are expressed in the first step of the viral life cycle to protect against emerging variants and zoonotic transfers of new pathogenic coronaviruses.

Our findings highlighted the potential for memory T cells targeting conserved regions of *coronaviridae* to determine the initial outcome of infection, an important extension to the traditional role for T cells in limiting disease pathology once infection is established. An early role for T cells in determining infection outcome has also been supported by the recent finding that HLA-B15 is enriched in cohorts with asymptomatic SARS-CoV-2 infection [10]. As in our study, these data suggested pre-existing cross-reactive memory T cells, likely generated by seasonal coronaviruses, were able to give a temporal advantage to rapid viral control.

For T cells to act quickly enough to abort infection, we postulated that some of the key specificities must be poised as sentinels at sites of viral inoculation. In support of this, we were able to identify SARS-CoV-2 cross-reactive T cells enriched within the T_{RM} pool of bronchoalveolar lavage samples obtained from healthy donor airways before the pandemic [7]. Pre-existing SARS-CoV-2-reactive T cells have also been identified in unexposed oropharyngeal lymphoid tissue and in nasal mucosa following breakthrough infection [11,12]. Depletion of airway-resident T cells has confirmed their vital contribution to *coronaviridae* control in animal models [13]. However intramuscular vaccination is not able to expand nasal or lower airway SARS-CoV-2-specific T cells in humans [11,14], underscoring the need for mucosal-targeted vaccines to harness the advantages of tissue-resident immunity.

In summary, our work has contributed to a growing body of evidence highlighting crucial roles for tissue-resident T cells in organ-specific immunity, including the response to prophylactic and therapeutic vaccines. Our findings suggest that tissue-resident HBV-specific T cells could provide long-lived immunosurveillance for functional cure. However, their efficient induction by therapeutic vaccination requires a better understanding of local cellular regulation, for example by the serial monitoring of liver-compartmentalised immunity that we have shown can be achieved using fine needle aspirates [15]. There is also a strong argument to target tissue-resident immunity in the next generation of prophylactic vaccines aiming to achieve infection-blocking pan-coronavirus immunity.

Declaration of Competing Interest

MK Maini has sat on advisory boards for Gilead Sciences, GSK, Astrivax and Roche and received unrestricted laboratory research funding from Gilead Sciences.

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