Skin resident T cells

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Therapeutic medicine

T<sub>RM</sub>-mediated diseases can theoretically occur due to pathological T<sub>RM</sub> cells or consequently to aberrant activation signals to the T<sub>RM</sub> cells. Even though, it becomes evident that T<sub>RM</sub> cells can promote certain diseases, such as psoriasis and vitiligo, the full pathogenicity and contributing mechanisms are not yet fully understood. In one way, targeting pathological T<sub>RM</sub> cells could be used to develop more effective therapies, since current therapies fail to cure patients permanently. However, it remains very difficult to selectively identify pathogenic T<sub>RM</sub> cells. Autoimmune diseases, like psoriasis, seem to be triggered by polyclonal populations of T<sub>RM</sub> cells, which have diverse T cell receptors (TCR) among distinct individuals. On the other hand, it may be easier to identify the pathological clone in oncological diseases, like mycosis fungoid, since it is often caused by a monoclonal subset capable to be identified by the TCR. Hence, novel therapies capable of selectively targeting clonal cells with a unique TCR could possibly cure many diseases. Unfortunately, we still lack techniques and knowledge to successfully generate and reproduce such approach.

Another approach could be to act on T<sub>RM</sub> signaling. For example, T<sub>RM</sub> cell development and T<sub>RM</sub> cell entry into the epidermis is shown to be highly dependent on IL-15.<sup>1,2</sup> Therefore, IL-15 inhibition could be used as targeted therapy for T<sub>RM</sub> cell-mediated diseases. One recent case study showed that inhibition of IL-15 in a patient with vitiligo resulted in substantial repigmentation.<sup>3</sup> Downregulation of IL-15 and IL-7 provided promising results in contact hypersensitivity in mice. IL-15 and IL-7 deficient mice showed reduced ear swelling and reduced lymphocytic infiltration, compared to the control group.<sup>2</sup> Furthermore, IL-7 is suggested as a target for cutaneous T cell lymphomas (CTCL), as mice with CD4<sup>+</sup> lymphoma show a reduction of malignant T<sub>RM</sub> cells when lacking IL-7. In human patients with CTCL, induced expression of IL-7 is seen.<sup>2</sup> Therefore, IL-7 might be useful in targeted treatment for CTCL. Other study demonstrated that the IFN-γ dependent chemokine CXCL10 as well as its receptor CXCR3 on autoreactive T<sub>RM</sub> cells, was upregulated in patients with vitiligo. Using a mouse model of vitiligo, it was possible to study the effect of targeting CXCR3 on T<sub>RM</sub> cells and its chemokine CXCL10. When mice received CXCR3<sup>−/−</sup> T cells or targeted therapy to CXCL10, or lacked CXCL10, they showed minimal depigmentation development. Strikingly, neutralizing CXCL10 on vitiligo mice with depigmented skin induces disease reversal as was visible by repigmentation of skin lesions.<sup>4</sup>
Follow-up studies are still needed to address the feasibility of these approaches. The systemic and long-term consequences of inhibiting or downregulating these cytokines remain unknown. Thereafter, could those therapies be safely and efficaciously translated into humans? Furthermore, it will be interesting to observe possible consequences of T_{RM} cell targeting therapies, such as opportunistic infections or cancer.

**Preventive medicine**

Since skin T_{RM} cells have shown to play an important role in pathogen elimination and creating an immunological memory, these T cells might be also essential for the development of new vaccine strategies. Various studies suggested that induction of T_{RM} cells in skin could lead to widespread host protection. Jiang at al. illustrated the ability of T_{RM} cells to control viral infection and form an extensive immunological memory in an experiment with mice vaccinated with vaccinia virus (VACV). Immunized mice were infected with VACV and treated with a S1P1 modulator to prevent circulating T cells to recruit at the infection site. Mice treated with S1P1 modulators, did not show different viral titers from untreated mice. Thus, T_{RM} cells are sufficient to protect against viral infection. Secondly, an immunized mice population was injected with VACV in one ear, after which the density of T_{RM} cell population was analyzed in both ears. This resulted in protection of the infected ear, but also accumulation of T_{RM} cells in the uninfected ear. Although T_{RM} cell concentrations predominate at the prior infection site, progressive increase of T_{RM} cells all over the skin surface was seen after multiple reinfections of various skin sites. These studies indicate that T_{RM} cells generate distributed skin protection against reinfection, even in absence of circulating T cells. However, retroperitoneal injection of VACV failed protecting against secondary skin infection. Thus, immunization of skin is dependent on specific immunization routes.

Another study found that skin scarification could lead to widespread immunity provided by different populations of T_{RM} cells. After scarification with VACV, T cells migrated towards skin draining lymph nodes. Most of these T cells showed expression of skin homing markers and migrated to the skin, where they long term reside as T_{RM} cells. However, some T cells obtained secondary tissue specific imprinting, enabling them to migrate towards distant epithelial tissues such as gut and lung. In those tissues they stayed resident, providing long term viral protection. Skin scarification was shown to be 100,000 times more effective than subcutaneous, intradermal and intramuscular vaccination. This demonstrates that skin immunization can cause widespread immunity by the distribution of different T_{RM} cell progenitor subsets and suggest an effective role for
TRM cells in vaccine-induced protection, by epidermal scarification rather than intramuscular injection.

Two studies found that TRM cells could provide long lived local protection against herpes simplex virus (HSV1 and HSV2). Mackay et al. showed that progression of HSV1 infection could not be inhibited by circulating memory T cells. In contrary, skin TRM cells provided long term epithelial immune protection. HSV1-specific T cells were embedded in the skin in response to nonspecific local inflammation of the skin, forming a population of TRM cells. After infection with HSV1, skin sites containing TRM cells did not develop herpetic lesions. Consistently, severe suppression of viral replication was seen in these skin sites. By using a prime and pull vaccine strategy, TRM cells were recruited to protect against genital HSV2 infection. In a study by Shin et al., mice were vaccinated parenterally to induce circulating T cell responses. Genital TRM cell recruitment was accomplished after topical chemokine was applied to the genital tract. In result, the migration of HSV2 virus towards sensory ganglia decreased and mice did not show HSV lesions after infection with HSV2.

Other study showed that protective immunity against chlamydia trachomatis could be induced by the development of circulating as well as resident T cells after vaccination. Inducement of TCM cells did not require specifically located vaccination, whereas only mucosal vaccination resulted in TRM cell induction.

In summary, the development of new treatments capable of identifying and targeting pathogenic TRM cells could finally cure patients from chronic diseases. Furthermore, vaccines are typically generated to induce systemic memory response, leading at times to insufficient protection. Recognizing TRM cells as strong providers of tissue-specific immunity may revolutionize vaccination strategies of the future. It is imperative to expand our understanding on TRM biology, pathogenicity and associated mechanisms of immune protection, in order to gain more effective treatments and reduce the incidence of infectious diseases.

REFERENCES

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