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ABSTRACt

055 CTD T cell immunity after respiratory viral infection is transient, while CD8 T cell immunity after epidermal vaccination is long focused and durable

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Pandemic respiratory viral pathogens like Influenza A and SARS-CoV2 exhibit continuous and existentially traumatic mutations, thus making cell-cell contact with the goal of anti-body-mediated protection elusive. CD8 T cells mediate eradication of viral disease, and vaccination to conserved internal viral proteins to elicit CD8 T cell memory is a promising strategy. Using a mouse model, we compared pulmonary infection with H1N1 influenza with skin (epidermal) vaccination using Modified Vaccinia Ankara (MVA) expressing highly conserved NP or another conserved Ags. H1N1 influenza pulmonary infection led to recruitment and lung infiltration with Ag specific CD8 T cells by day 5-10. By day 40, abundant CD8 lung T and LNs were present. Surprisingly, by day 60, both lung T and systemic T cells were greatly diminished and were absent at day 120. These mice were protected against lethal challenge at day 40 but not day 80, suggesting built-in obsolescence of CD8 memory. In contrast, epidermal vaccination led to CD8 T cell infiltration of lung at day 5-10, measurable at day 30, and still detectable at day 80 in lung, LN and spleen. In addition, a novel intravascular lung population of CD8 T cells was present at all time points. These mice were completely protected against lethal flu challenge at day 80 and 120. Protection was observed after pulmonary challenge with either H1N1 or H1N2 influenza as well as in B cell depleted mice. We analyzed protective immunity in skin vaccinated mice. At 2 hours after pulmonary challenge, Ag specific CD8 T cells moved from the intravascular space into the lung parenchyma, becoming abundant at day 1, and persisted for at least 80 days. Single cell RNA sequencing indicated that these intravascular T cells were transcriptionally distinct from systemic T and N cells. We conclude that CD8 T cell immunity after pulmonary infection is powerful but short-lived, while skin vaccine induced CD8 T cell protective immunity is mediated by lung intravascular T cells is protective and durable.

056 IL-15 prolongs hair growth and operates as a guardian of human hair follicle immune privilege

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Tissue-resident memory T cells (TResM Ts) in the skin and hairfollicle (HF) microenvironment have been described as soldiers of human hair follicle immune privilege. Recent findings revealed IL-15 as a major player in the development and maintenance of TResM Ts, and new IL-15Ra signaling pathways were identified. IL-15 prolongs hair follicle cycles, operates as a guardian of immune privilege, and exhibits a unique function in the hair follicle. IL-15 is expressed in the epidermis, outer root sheath (ORS), and inner root sheath (IRS), and is critical for the development and maintenance of TResM Ts in the skin. The unique expression pattern of IL-15 in the skin suggests that it may play a role in the maintenance of immune privilege. Our recent studies revealed that IL-15 is expressed in the epidermis, ORS, and IRS, and is critical for the development and maintenance of TResM Ts in the skin. The unique expression pattern of IL-15 in the skin suggests that it may play a role in the maintenance of immune privilege.

057 Targeting keratinocytes to potentiate skin immunization

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Skin is a unique target for vaccination. Targeting keratinocytes to produce proinflammatory mediators to improve immunity is rational approach for vaccine design. Keratinocytes genetically engineered to overexpress the stress response related transcription factor x-box binding protein 1 (XBP1) increased production of proinflammatory mediators and co-delivered antigen. Keratinocyte-specific overexpression of XBP1 through cutaneous genetic immunization was transient and induced a pro-immunogenic skin microenvironment, including enhanced expression of proinflammatory mediators and co-delivered antigen, and increased skin-infiltration and stimulatory function of dendritic cells. Overexpression of XBP1 in keratinocytes can provide a vaccine to enhance induction of antigen-specific humoral and cellular immune responses, including durable antigen-specific skin-resident memory CD8 T cells and effective protective immunity in mouse tumor models. These findings support the strategy of targeting keratinocytes to improve skin immunization, identify XBP1 as a potential molecular ‘adjuvant’ in skin immunization, and contribute to the development of CD8 T cells and effective protective immunity in mouse tumor models. These findings support the strategy of targeting keratinocytes to improve skin immunization, identify XBP1 as a potential molecular ‘adjuvant’ in skin immunization, and contribute to the development of CD8 T cells and effective protective immunity in mouse tumor models.

058 Heterogeneity and lineage development of memory CD8+ T cells after viral infection of skin

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To better understand memory CD8 T cell development, we analyzed the profile of CD8+ T cells infiltrating skin as well as their circulating counterparts in the dLN after the same VACV skin infection at days 2-60, using the droplet-based microfluidic system Chromium (10X Genomics) single cell RNA sequencing platform. Using the Lesiden algorithm, Ag-specific CD8 T cells were clustered and mapped through uniform manifold approximation and projection. Early activated T cells clustered together, showing a unique transcriptional profile, and skin and LN effectors began to diverge at day 5. A population of T cells with high expression of CD38 was observed at day 5, and then decreased in the following days. These results suggested that early activated CD8 T cells may play a role in the initial stages of the immune response. By day 30, a distinct population of CD8 T cells with high expression of CD44 was observed, which may represent the memory CD8 T cell population. By day 60, a unique population of CD8 T cells with high expression of the activation marker CD69 was observed, which may represent the effector memory CD8 T cell population. These findings suggested that there is a time-course for CD8 T cell differentiation, with early activated CD8 T cells differentiating into memory and effector CD8 T cells over time.

059 Enhanced and suppressed tumor immunity is mediated by IL-1R1 on distinct immune cells

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Inflammation is necessary for immune defense against pathogens and a functional antitumor immune response to eradicate chronic inflammation promotes tumor growth and promotes escape from immune-mediated destruction. Recently, we and others demonstrated that deficiency of IL1β strongly favors antitumor immunity, and multiple clinical trials involving antibody-mediated IL1β blockade in multiple cancers are underway. The mechanism, however, remains obscure. We demonstrated that intact IL1β signaling is required for IL1β blockade-induced antitumor immunity, leading to the hypothesis that its interaction with the IL1 type I receptor (IL1R1) and subsequent signaling was required for the antitumor immune response. To determine which cell type required the IL1R1 signal, we studied the antitumor immune response in several mouse models. IL1β protein expression of both, the private IL-15 receptor (IL-15Ra, which is not stimulated by IL-15) and costimulation of T cells provokes anti-tumor response. To determine the antitumor immune response, the IL1 type I receptor (IL1R1) and subsequent signaling was required for the antitumor immune response. To determine the antitumor immune response, the IL1 type I receptor (IL1R1) and subsequent signaling was required for the antitumor immune response. To determine the antitumor immune response, the IL1 type I receptor (IL1R1) and subsequent signaling was required for the antitumor immune response.