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RESEARCH HIGHLIGHT

Tissue-resident memory T cells keep cancer dormant

Sarah Sharon Gabriel[1] and Axel Kallies[1]

Cell Research (2019) 29:341–342; https://doi.org/10.1038/s41422-019-0156-5

Cancer-immune equilibrium is a state in which low numbers of cancerous cells are kept in an occult or dormant state by the immune system for long periods. A recent study by Park et al. published in *Nature* found that tissue-resident CD8+ memory cells actively enforce cancer dormancy of epicutaneous melanomas.

The importance of the adaptive immune system in controlling tumor growth and metastasis is unquestioned. Increased numbers of T cells, in particular CD8+ tumor infiltrating lymphocytes (TILs), are generally associated with a better survival prognosis of patients.[1] However, CD8+ TILs often express inhibitory receptors such as PD-1 and Tim3 resulting in partial dysfunction, a state known as exhaustion.[2] Checkpoint blockade that targets inhibitory receptors can remove the 'brake' from exhausted cells and has proven successful in reinvigorating the T cell response in many cancers, highlighting the importance of CD8+ cells in tumor control.[3] Importantly, malignant transformation does not necessarily result in clinically manifest cancer. Indeed, there is ample evidence for the ability of the immune system to successfully keep tumors in a subclinical state for long periods of time, without eradicating the malignant cells completely. This state of tumor control is termed cancer-immune equilibrium. The precise mechanisms of this prolonged immune surveillance and the role of CD8+ cells in this process have remained ill-defined.[4] The recent publication by Park et al. in *Nature* showed that tissue-resident memory T cells (T_{RM}) are key players in keeping tumors in a dormant state and thus are critical for establishing cancer-immune equilibrium (Fig. 1).[5]

T_{RM} are generated in response to systemic or local infections and, in contrast to their circulatory counterparts, they persist locally in peripheral non-lymphoid tissues. They have attracted increased attention in recent years as they are critical in providing the first line of adaptive immune protection at portals of pathogen entry such as the skin, lung or gastrointestinal tract.[6] T_{RM} express a characteristic set of surface molecules, including the tissue retention molecule CD69, and have been described in virtually every organ analyzed both in humans and mice. Skin-resident T_{RM} that express the integrin CD103 are particularly well characterized[6] and are central to the work by Park et al. To study the equilibrium between tumor cells and the immune system, Park et al. took advantage of a novel murine cancer model where melanoma cells were transplanted directly into the epidermal layer of the skin, the anatomical location where melanomas naturally arise.[5,7] In this model only ~60% of mice developed macroscopic cancers within the first four weeks of inoculation. The remaining mice either cleared the tumor or controlled its growth for long periods. This is in stark contrast to the widely used subcutaneous melanoma model which shows a penetrance of close to 100%, but does not reflect the physiological site of melanoma origin. Thus, the epicutaneous melanoma model utilized by Park et al. offered the unique opportunity to study and image the interaction of local immune cells with dormant tumor cells in a physiologically relevant setting. Intriguingly, mice that developed macroscopic tumors in this setting had much fewer antigen-specific CD8+ T cells in and around the tumor tissue when compared to mice that were able to control tumor outgrowth. Given the limited access of circulatory T cells to the epidermis, the authors reasoned that epicutaneous T_{RM} might be responsible for maintaining the observed cancer-immune equilibrium. Indeed, antigen-specific cells accumulated in close proximity to melanoma cells and expressed the skin T_{RM} surface markers CD69 and CD103. In addition, intravital microscopy showed that most antigen-specific CD8+ cells were located in the epidermis and displayed surveying behavior towards the cancer cells, characteristics previously described for skin T_{RM}. Using TCR transgenic T cells with relevant T cell receptors towards the cancer in combination with techniques that selectively depleted either circulating memory T cells or T_{RM}, Park et al. were able to demonstrate that antigen-specific T_{RM} were functionally critical in controlling the dormancy of cancer cells.

Interestingly, phenotypic comparison of antigen-specific cells infiltrating macroscopic tumors and those located in the skin surrounding the tumors showed that TILs displayed higher expression of exhaustion markers such as TIGIT, CTLA4 and PD-1 and lower expression of CD69 and CD103 compared to T_{RM} in the skin. These phenotypic differences suggest that T_{RM} and TILs represent different developmental trajectories or differentiation stages. T_{RM} that are present already at very early stages of tumor development appear to be able to maintain their functionality. In contrast, TILs found within the tumor may become functionally exhausted due to their exposure to high amounts of tumor-associated antigen. It remains to be clarified to what degree T_{RM} are able to infiltrate the tumor mass itself and exercise control within the tumor. Furthermore, the relationship between T_{RM} and TILs is unclear, T_{RM} may be terminally differentiated or they may constitute a progenitor population for TILs at later stages of the disease.

While several studies have shown a positive correlation between patient outcome and the presence of T cells with T_{RM} phenotype in the tumor,[8,9] the precise role of T_{RM} in tumor immunity has remained controversial. The study by Park et al. is the first to systematically examine the role of T_{RM} in the early stages of tumor growth, to visualize in detail the interaction of T_{RM} with tumorous cells and thus to demonstrate the critical role of CD8+ T_{RM} in immune surveillance during the equilibrium state of cancer development. Carcinomas make up the vast

[1]Department of Microbiology and Immunology, The Peter Doherty Institute for Infection and Immunity, University of Melbourne, Melbourne, Australia
Correspondence: Axel Kallies (axel.kallies@unimelb.edu.au)

Published online: 15 March 2019

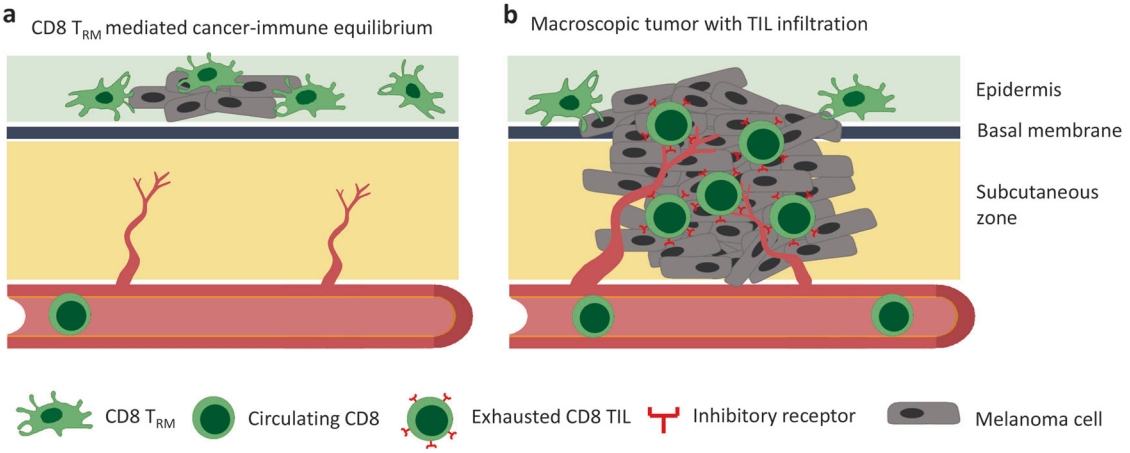

Fig. 1 **a** Tissue-resident CD8 memory cells (T_{RM}) in the epidermal layer of the skin actively control subclinical melanomas for prolonged periods of time, thereby establishing and maintaining cancer-immune equilibrium. Circulatory T cells are largely excluded from the epidermis, the location where melanomas naturally arise. **b** During later stages of the disease, the vascularized tumor mass is infiltrated by CD8 T cells (tumor infiltrating lymphocytes, TILs) that often express inhibitory receptors such as PD-1 and show an exhausted phenotype

majority of cancers and at least in early stages their epidermal location precludes immune-control through circulatory cells. Thus, the described mechanism of T_{RM}-mediated cancer-immune equilibrium is of fundamental importance. Cancers can remain dormant for many years and relapses in patients can occur after decades of remission.[10] Better understanding of T_{RM} biology and of the tumor control mechanisms involving T_{RM} might pave the path for the development of therapies aimed at boosting local T_{RM} populations, for example after surgical tumor removal.

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