type of skin cancer, and later on cancers of breast, prostate, ovaries, and colon have shown that patient survival was significantly extended when tumors harbored a high abundance of CD8+ T cells. These studies provided compelling evidence that CD8+ T cells are in principle able to protect against cancer.

Researchers established that CD8+ T cells isolated from tumors and cultured in vitro for several days to weeks could specifically detect and kill cancer cells. But a decade ago, we found that these cells targeted cancer relatively poorly when tested immediately after their isolation from tumors. This indicated that, while tumor-reactive CD8+ T cells manage to get into tumors, the tumor environment somehow prevents the cells from efficiently killing tumor cells.

Then, an unusual feature of tumorspecific CD8+ T cells offered a clue to the reason for that waning effectiveness. The immune cells expressed receptors known as checkpoints that decreased, rather than improved, the capacity of CD8+ T cells to kill tumor cells. The importance of such cell-surface receptors in dampening the function of T cells was first recognized separately by Yasuaki Honjo and James Allison in the 1990s. Their pioneering work, for which they were awarded the Nobel Prize in Physiology or Medicine in 2018, led to the development of antibodies that prevent inhibitory receptors, such as programmed death 1 (PD-1), from engaging their binding partners present on other cells. This tweak improved the function of CD8+ T cells in vitro.

Blocking inhibitory receptors has revolutionized the treatment of several cancers, including melanoma and certain types of lung, bladder, kidney, intestinal, and gynecological cancers. Metastatic melanoma, which formerly was untreatable, can now be cured in a significant fraction of patients thanks to these immunotherapies. When the inhibitory PD-1 receptor is blocked by treatment with antibodies, CD8+ T cells present in the tumor increase expression of the cytotoxic granzyme B protein, a hallmark of killer cells, and start to multiply; this is often associated with tumor shrinkage and therapy success. However, PD-1 expressing CD8+ T cells present in tumors were thought to be “exhausted” and unable to divide. It was thus difficult for immunologists to understand the full cellular and molecular basis for the CD8+ T cell expansion in response to checkpoint blockade. It was also unclear why the therapy was effective for some patients but not others.

Science often does not follow a linear path, and important new insights frequently derive from studying seemingly unrelated problems. For example, exhausted CD8+ T cells were first described in chronic viral infections more than 20 years ago. More recently, detailed analyses of virus-fighting T cells by us and by Rafi Ahmed’s group at Emory University revealed that there are at least two distinct types of CD8+ T cells. A rare cell type does not engage directly with infected cells but rather sustains the CD8+ T cell response to infection by renewing itself and by dividing to form the more common type of CD8+ T cells that has the potential to kill virus-infected cells.

These findings raised the possibility that a similar division of labor among CD8+ T cells exists in tumors, and that this plays a role in the mechanisms of tumor immunotherapy.

CHECKPOINT INHIBITORS AND STEM-LIKE T CELLS

The body’s defense system against infection also fights tumors, generating tumor resident stem-like T cells and killer T cells that express inhibitory receptors such as PD-1. When PD-1 binds to PD-L1 or PD-L2 on tumor cells or other cells, T cell functions are subdued. Checkpoint blockade treatments interrupt this interaction. This allows stem-like T cells to proliferate and to produce new killer T cells that can now kill tumor cells.

While tumor-reactive CD8+ T cells manage to get into tumors, the tumor environment somehow prevents the cells from efficiently killing tumor cells. Tumors harbor stem cell-like CD8+ T cells that express PD-1

Two recent papers, one by us and one from Nick Haining’s group at Harvard Medical School, used mouse models to look for different types of PD-1 expressing CD8+ T cells in tumors and found that there are indeed two main subsets of cells: one that produces granzyme B, a hallmark of cell-killing CD8+ T cells, and one that does not make granzyme B but instead expresses T cell factor 1 (TCF1), a transcription factor that confers stemness properties to T cells.