in vitro and in vivo. Exposure to NO was shown to cause a drop in the ATP:ADP ratio in activated macrophages, suggesting this could be responsible for suppressing their cytokine-producing capacity. In support of this idea, decreasing ATP:ADP ratios in macrophages through inhibition of ATP synthase also dampened their cytokine production. Moreover, iNOS inhibition in vivo led to increased cellular ATP:ADP ratios in monocyte-derived cells isolated from *L. major*-infected skin tissue.

Finally, the authors addressed whether NO supresses macrophage respiration in a cell-autonomous manner or acts more broadly in the tissue. In in vitro experiments using mixtures of wild-type and iNOS-deficient macrophages, inhibition of cell respiration increased according to the density of NO-producing cells. Only a minor blockade of cell respiration and cytokine production was seen in NO-producing cells when they were present at low densities compared with iNOS-deficient cells (1:9 ratio); however, cell respiration and cytokine secretion was effectively blocked in iNOS-deficient macrophages surrounded by equal numbers of iNOS-competent cells (1:1 ratio). Similar findings were made in *L. major*-infected mice that had been reconstituted with different ratios of iNOS-deficient and iNOS-competent bone marrow cells.

Therefore, the suppressive effect of NO appears to rely on NO diffusion in the tissue and NO only downregulates the inflammatory response when a sufficient density of NO-producing cells is present in the tissue. This quorum-sensing mechanism is likely to be important for preventing excessive inflammatory responses that could lead to tissue pathology.

Yvonne Bordon

ORIGINAL ARTICLE Postat, J. et al. A metabolism-based quorum-sensing mechanism contributes to termination of inflammatory responses. *Immunity* https://doi.org/10.1016/j.immuni.2018.07.014 (2018)
FURTHER READING Antonioli, L. et al. Quorum-sensing in the immune system. *Nat. Rev. Immunol.* **18**, 537–538 (2018)

NKILA shRNA or an empty vector into immunocompromised mice bearing established human breast cancer xenografts. Adoptive transfer of CTLs with *NKILA* knockdown efficiently inhibited tumour growth and was associated with increased CTL cytotoxicity, NF-κB activity and expression of anti-apoptotic genes compared with the control T cell transfer.

Returning to the patients, it was shown that NKILA is expressed at higher levels in CTLs and T_H1 cells (in particular, in those expressing IFNγ) than in T_{reg} cells and T_H2 cells from patients with breast cancer. High NKILA expression in tumour-specific CTLs correlated with less infiltration into tumours and larger tumour size, and patients with a higher percentage of $NKILA^{hi}$ CTLs had shorter overall survival.

So how is NKILA expression regulated? The findings that JAK–signal transducer and activator of transcription (STAT) signalling was increased in tumour-antigen-activated CTLs, that inhibitors of STAT1 completely abrogated NKILA upregulation in activated T cells and that STAT1 activity differed among tumour-infiltrating T cell subsets suggested a role for STAT1. Indeed, STAT1 was found to bind near the *NKILA* transcription start site and activation of STAT1 by IFNγ led to upregulation of NKILA. Finally, STAT1-mediated *NKILA* transcription was shown to be controlled by calmodulin downstream of TCR-induced calcium signalling. Antigen stimulation of CTLs substantially increases the acetylation of histones at the *NKILA* promoter region, thus opening the chromatin to allow STAT1 binding and transcription of *NKILA*. In unactivated T cells, histone deacetylases (HDACs) occupy the *NKILA* promoter and block STAT1 access, but following TCR stimulation, activated calmodulin removes HDACs from the *NKILA* promoter to allow STAT1-mediated *NKILA* transcription.

So, this study shows for the first time that targeting a lncRNA to protect immune cells from AICD could be a feasible approach to improve adoptive T cell therapy.

Lucy Bird

ORIGINAL ARTICLE Huang, D. et al. NKILA lncRNA promotes tumor immune evasion by sensitizing T cells to activation-induced cell death. *Nat. Immunol.* **19**, 1112–1125 (2018)

Journal club

MAKING NEW MEMORIES

Although the existence of memory T cells in peripheral tissues had long been recognized, it was not known for many years whether these cells were truly tissue resident. Memory T cells had classically been divided into effector memory T (T_{EM}) cells and central memory T (T_{CM}) cells, and it was largely thought that tissue T cells comprised T_{EM} cells in transit through the body. However, it was postulated by David Masopust, Leo Lefrançois and colleagues in 2001 that memory T cells in tissues "either continuously recirculate through peripheral tissues or permanently reside in them" (Masopust et al., 2001). Landmark papers by Gebhardt et al. and Masopust et al., published in 2009 and 2010, signified the advent of tissue-resident memory T (T_{RM}) cells as a distinct T cell subset.

These two studies extended the T_{EM} and T_{CM} cell paradigm by showing that tissue T cells exist in disequilibrium with the circulating T cell populations. They showed that antigen-specific $CD8^+$ T cells with a unique phenotype persist at the site of previous infection — namely, the dorsal root ganglia and skin of herpes simplex virus-infected mice or the intestinal epithelium following infection with lymphocytic choriomeningitis virus. Coincidentally, figure 5 of both papers is central, showing that T_{RM} cells can persist for several weeks as an autonomous population following tissue transplantation. Other studies had provided evidence in support of tissue residency (Boyman et al., 2004), but it was the study by Gebhardt et al. that showed that these T_{RM} cells afford enhanced local protection, which is the defining feature of immunological memory.

Collectively, these studies were instrumental in spawning a renewed focus on regional immunity, persuading me and many others to work in the field of tissue-resident memory. The concept of tissue residency has now been expanded to other lymphocyte populations, even those of the innate immune system, such as natural killer T cells and innate lymphoid cells. The importance of T_{RM} cells is now well accepted and they are emerging as key players in the fight against infection. Their manipulation in therapeutic settings has enormous potential for the clinical modulation of tissue pathologies and has considerable promise for the control of solid organ cancers.

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The author declares no competing interests

ORIGINAL ARTICLES Gebhardt, T. et al. Memory T cells in nonlymphoid tissue that provide enhanced local immunity during infection with herpes simplex virus. *Nat. Immunol.* **10**, 524–530 (2009) | Masopust, D. et al. Dynamic T cell migration program provides resident memory within intestinal epithelium. *J. Exp. Med.* **207**, 553–564 (2010)
FURTHER READING Masopust, D. et al. Preferential localization of effector memory cells in nonlymphoid tissue. *Science* **291**, 2413–2417 (2001) | Boyman, O. et al. Spontaneous development of psoriasis in a new animal model shows an essential role for resident T cells and tumor necrosis factor-α. *J. Exp. Med.* **199**, 731–736 (2004)