Therefore, the authors propose that CCR5AS stabilizes *CCR5* mRNA by sequestering RALY. In keeping with this, the association between RALY and *CCR5* mRNA was markedly increased in Hut-78 cells with knockdown of CCR5AS expression. Furthermore, *CCR5* mRNA decay was slower in cells with knockdown of RALY expression, which suggests that binding of RALY to *CCR5* results in its degradation.

Overall, the data indicate that increased expression of CCR5AS (owing to the rs1015164A allele) results in increased expression of CCR5 by sequestering RALY. The final piece of the puzzle involved explaining how the rs1015164A allele increases CCR5AS expression given that this SNP does not seem to be in a transcription factor binding site. They showed that rs1015164 is in linkage disequilibrium with rs2027820, which is located in the first intron of CCR5AS. The rs2027820G allele (in linkage disequilibrium with rs1015164A) has an intact transcription factor binding site for ATF1, whereas the rs2027820A allele (in linkage disequilibrium with rs1015164G) disrupts the transcription factor binding site and results in decreased CCR5AS expression.

The relevance of CCR5AS expression level to HIV infection of $CD4^+$ T cells was tested in an in vitro assay using CCR5-dependent and CCR5-independent HIV-1 vectors encoding green fluorescent protein (GFP). CCR5AS knockdown led to a decreased proportion of GFP^+ cells in cultures infected with CCR5-dependent virus but not CCR5-independent virus. Similarly, primary $CD4^+$ T cells from rs1015164AA/AG donors were more susceptible to infection with CCR5-dependent virus than rs1015164GG donors.

The results provide a biological explanation for the association between rs1015164A/G and outcome of HIV infection and suggest that similar mechanisms involving lncRNAs could explain the disease associations of other intergenic SNPs.

Kirsty Minton

ORIGINAL ARTICLE Kulkarni, S. et al. CCR5AS lncRNA variation differentially regulates CCR5, influencing HIV disease outcome. *Nat. Immunol.* **20**, 824–834 (2019)

invariant T cells, as well as a subset referred to as double-negative αβ T cells by the authors, but only polarization of the double-negative subset was altered in the absence of neutrophils.

Expression analysis revealed that unconventional T cells produced more IFNγ in vitro in response to IL-12 plus IL-18 than did conventional T cells, and in vivo neutralization of IL-12 skewed the polarization of wild-type unconventional T cells to a T-bet^{low} phenotype. In co-cultures, neutrophils amplified IL-12 production by macrophages in response to triggering by cytokines and Toll-like receptor 9 agonist. The amount of IL-12 produced in this experimental setting was sufficient to trigger IFNγ production by unconventional T cells but not by conventional T cells, which together supports a type 1 antitumour pathway involving collaboration between neutrophils, macrophages and unconventional T cells.

Delving deeper into the diversity of the tumour-associated unconventional T cell populations using single-cell RNA sequencing, the authors identified 12 cell clusters with specific gene signatures. Lack of *Csf3r* was associated with selective depletion of a double-negative subset with an innate-like phenotype ($Ly49^+$), type 1 polarization and cytotoxic potential. Co-transfer of this subset and tumour cells markedly reduced tumour growth in vivo.

Finally, they showed that this neutrophil-dependent pathway is relevant to certain human tumours. Neutrophil and type 1 (*IFNG* and *CSF3R*) gene signatures were associated with better survival in patients with undifferentiated pleomorphic sarcoma (which is closely modelled by 3-MCA-induced sarcomas in mice) and also in patients with colorectal cancer but not with other sarcoma types.

In summary, this study highlights a new mechanism of immune resistance in selected tumours and an important role for unconventional T cells that has not been fully appreciated.

Lucy Bird

ORIGINAL ARTICLE Ponzetta, A. et al. Neutrophils driving unconventional T cells mediate resistance against murine sarcomas and selected human tumors. *Cell* https://doi.org/10.1016/j.cell.2019.05.047 (2019)

Journal club

THE POWER OF DESCRIPTION

Understanding the molecular mechanisms that underpin homeostasis and disease is of crucial importance. Rational and precise preventive and therapeutic strategies depend on it. And indeed, facilitated by the staggering pace at which new technologies are evolving, it is becoming easier to interrogate molecular processes almost by the day. From time to time, however, it might be worth remembering that plain, careful and purely descriptive research can be — and indeed has been — the foundation of transforming molecular insight and huge clinical progress. The 1984 *Lancet* publication by Barry Marshall and Robin Warren, who were awarded the Nobel Prize in Physiology or Medicine for their work, is a prime example of this.

In this seminal paper, they describe the presence of small, Gram-negative, spiral or curved bacteria in the antral mucosa of roughly half of their 100 prospectively sampled patients presenting for gastroscopy. Very accurately, they report these bacteria as "appearing to be a new species related to the genus *Campylobacter*" and that signs of inflammation are seen at sites where the bacteria reside. Their detailed description led them to propose that these bacteria might be a key factor contributing to active chronic gastritis, and gastric and duodenal ulcers, which challenged the prevailing dogma that this group of disorders is caused by gastric acid. By extension, this observation also pointed to a link between infection, inflammation and the development of cancer — thus pioneering yet another hugely important conceptual framework.

> “bacteria might be a key factor contributing to active chronic gastritis, and gastric and duodenal ulcers”

Their unpretentious paper relied solely on light microscopy and minced tissue cultured on blood and chocolate agar — and on NOT working during the Easter holiday (“At first plates were discarded after 2 days but when the first positive plate was noted after it had been left in the incubator for 6 days during the Easter holiday, cultures were done for 4 days.”). Thus, a descriptive study, made by two prepared, well-rested and outstanding minds, has changed how we think about infection, inflammation and cancer, fuelling numerous mechanistic reports and benefiting countless patients. A great teaching case on more than one level, I believe.

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ORIGINAL ARTICLE Marshall, B. J. & Warren, J. R. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet* **323**, 1311–1315 (1984)