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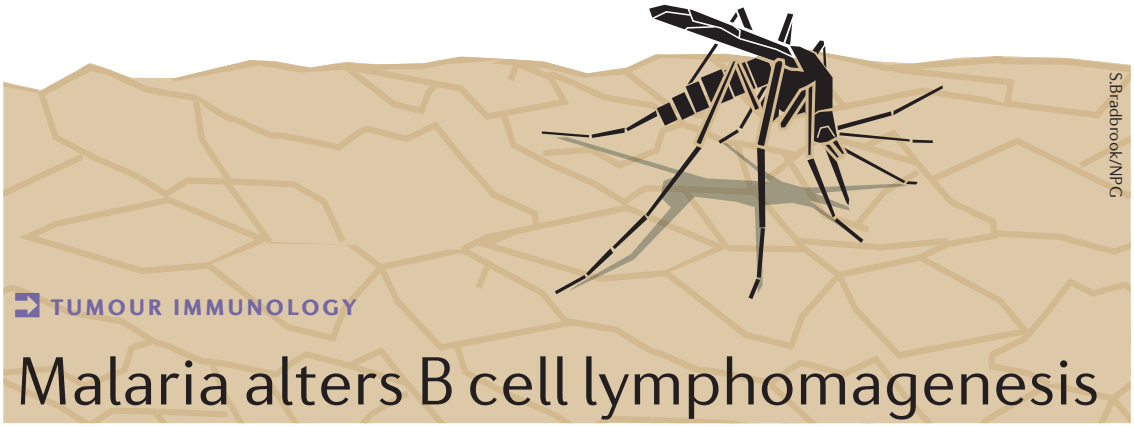

TUMOUR IMMUNOLOGY

Malaria alters B cell lymphomagenesis

Endemic Burkitt lymphoma is derived from germinal centre (GC) B cells and is common in sub-Saharan regions of Africa. Chronic infection with the human malarial parasite *Plasmodium falciparum* has been epidemiologically linked to endemic Burkitt lymphoma, but whether infection promotes lymphomagenesis has been unclear. Robbiani *et al.* now report that although *Plasmodium* infection does not affect the incidence of lymphoma, it does favour the development of mature B cell lymphoma that is dependent on activation-induced cytidine deaminase (AID), the enzyme involved in somatic hypermutation and class-switch recombination.

Plasmodium chabaudi was used to establish chronic malaria infection in wild-type mice. The infection was associated with an increased number of spleen cells, including B cells, and a prolonged expansion of GC B cell numbers. Furthermore, the authors found that AID expression was restricted to *P. chabaudi*-induced GC B cells, although malaria is known to induce widespread B cell activation.

Next, the authors mapped the DNA damage caused by *P. chabaudi* infection *in vivo* by determining genome-wide translocations in AID-deficient and AID-overexpressing mice. In both strains of mice, they identified widespread chromosome translocations in malaria-infected GC B cells, and the rearrangements were greatly increased in genic regions and highly transcribed genes.

Endemic Burkitt lymphoma is not only associated with dysregulated *MYC* expression but also bears frequent mutation of the tumour suppressor p53. To model this phenomenon, the authors generated p53-deficient B cells in either AID-deficient or AID-sufficient mice. All of the malaria-infected wild-type mice survived, whereas the two p53-deficient groups of mice died within 58–60 weeks. All of the p53-deficient AID-sufficient mice developed lymphoma, whereas only one-third of the p53- and AID-deficient mice did so. Most AID-deficient mice had enlarged spleens associated with extramedullary haematopoiesis but showed no histological evidence of cancer. Instead, these mice showed persistent parasitaemia and low red blood cell counts. Of note, AID was required to control parasitaemia in the chronic phase but did not alter acute infection. Thus, AID promotes *Plasmodium*-induced lymphomagenesis and is required to control chronic malaria infection.

Finally, the authors characterized the phenotype of the lymphomas developingin p53-deficient AID-sufficient mice. Both infected and uninfected mice developed lymphomas, but in the *P. chabaudi*-infected mice the B cell lymphomas were mainly of GC origin, whereas the uninfected mice developed pre-GC lymphoma. Furthermore, the authors found that the malaria-induced lymphomas had multiple translocations, many of which involved AID targets and were characteristic of human Burkitt lymphoma. Hence, malaria infection causes a shift towards a more mature, post-GC lymphoma phenotype, and the GC B cells elicited during infection have experienced widespread DNA damage.

These data show that *Plasmodium* infection alone does not induce cancer, but the infection promotes prolonged expansion of GCs containing AID-expressing B cells and a more mature lymphoma phenotype.

Elisabeth Kugelberg

> “AID promotes *Plasmodium*-induced lymphoma-genesis”

ORIGINAL RESEARCH PAPER
Robbiani, D. F. *et al. Plasmodium* infection promotes genomic instability and AID-dependent B cell lymphoma. *Cell* **162**, 727–737 (2015)