

# inside **blood**

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## ● ● ● IMMUNOBIOLOGY

Comment on Bains et al, page 5480

## Be fruitful, multiply, and replenish

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In this issue, Bains and colleagues show that T-cell proliferation plays a major role in the establishment of the T-cell pool, even in the very young, despite their high thymus output.

**B**ecause the size of the thymus in children is much larger than in adults, thymus output is widely believed to be responsible for the development of the peripheral T-cell pool during childhood. This idea is strengthened by the associations between age and the rate of T-cell reconstitution in lymphopenic patients,<sup>1</sup> and between thymus involution and decreasing naive T-cell numbers per microliter of blood. These arguments are indirect however, and do not take into account any changes in blood volume that occur upon growth of the body during childhood.<sup>2</sup> We have previously shown that—despite the gradual decline in naive T-cell numbers per microliter of blood—total body naive T-cell numbers in fact increase in early life.<sup>3</sup>

In this issue of *Blood*, Bains et al<sup>4</sup> present a mathematical model that integrates various experimental findings on naive T cells and T-cell receptor excision circle (TREC) dynamics<sup>5</sup> as well as thymus output<sup>6</sup> in young humans up to 20 years of age. They show that at all ages—even in the very young, when thy-

mus output is still at its maximum—the contribution of peripheral T-cell proliferation to the establishment of the naive T-cell pool prevails over thymus production. These findings are in line with the observation that in young healthy people, naive T-cell numbers increase while total TREC numbers do not, implying that peripheral T-cell proliferation contributes considerably to the establishment of the naive T-cell pool in early childhood.<sup>3</sup> Combining the decreasing output of the thymus with the increase of total body naive CD4<sup>+</sup> T-cell numbers during childhood, one would perhaps expect the rate of peripheral T-cell proliferation to increase with age. The study by Bains et al shows, however, that the rate of peripheral T-cell proliferation decreases when thymus output declines, concomitant with increasing naive T-lymphocyte residence times.

Despite the undisputed role of thymus involution during aging, the contribution of peripheral T-cell proliferation to the establishment of the naive T-cell pool is thus much

larger than previously thought, especially in the very young. Bains et al thereby demonstrate the risk of indirect intuitive reasoning and the strength of collective analysis of experimental data with the help of mathematical modeling.<sup>7</sup> The strength of their modeling approach is that it makes no a priori assumptions on how lymphocyte proliferation and death rates are affected by age or by total lympho-

cyte numbers. Provided that the average TREC content of naive T cells stays constant between birth and the age of 20, no other conclusions could be drawn from the data. The amount of naive T-cell TREC content data are, however, very limited, and TREC measurements are notorious for interassay variation. Therefore, this study also calls for more extensive measurement of TREC changes in naive T cells during childhood and warrants more direct measures of T-cell death rates in children, for example, based on stable-isotope labeling.

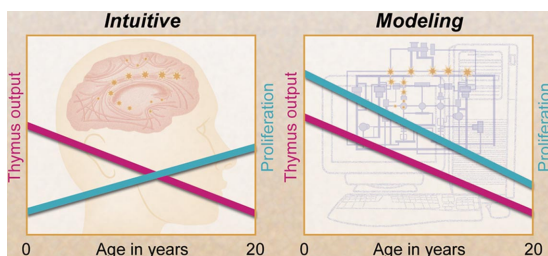
The large contribution of peripheral T-cell proliferation to the establishment of the naive T-cell pool in children goes against current beliefs, which may in part stem from improper extrapolation of insights obtained from young thymectomized mice. Even though lymphocyte dynamics in young and old mice are widely believed to be comparable to those in young and old humans, there is little data showing that such extrapolations can indeed safely be made. Similar comparative studies in mice of different ages and in humans older than 20 years of age should point out whether the processes responsible for the establishment and maintenance of the naive T-cell pool in mice and men are indeed comparable.

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Contrary to intuition, mathematical modeling by Bains and colleagues has shown that T-cell proliferation declines with age and, at any age during childhood, contributes more to the naive T-cell pool than thymus output. Professional illustration by A. Y. Chen.

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● ● ● CLINICAL TRIALS

Comment on Landgren et al, page 5412, and Weiss et al, page 5418

## Are all myelomas preceded by MGUS?

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In this issue of *Blood*, 2 independent articles report for the first time that an MGUS virtually precedes all cases on multiple myeloma.

**K**yle coined the term “monoclonal gammopathy of undetermined significance” (MGUS) for a condition that consists of a serum M-protein lower than 3 g/dL and less than 10% bone marrow plasma cells (BMPCs) in the absence of clinical manifestations due to the monoclonal gammopathy.<sup>1</sup> What we know about MGUS is (1) a high prevalence of 3.2% and 5.3% in persons older than 50 and 70 years, respectively, (2) the plasma cell clone has genetic and phenotypic profiles similar to myelomatous plasma cells, and (3) the average transformation rate to a malignant plasma cell disorder is 1% to 1.5% per year with actuarial probabilities of progression at 10 years of follow-up ranging from 12% to 17% and at 20 years from 25% to 34%. We also know that the factors associated with a higher probability of MGUS progression are M-protein concentration, proportion of BMPCs, IgA isotype, abnormal immunoglobulin free light chain (FLC) ratio, ratio between phenotypically aberrant and normal BMPC, and evolution pattern: “evolving” versus “nonevolving.”<sup>2-6</sup> However, there are a number of unknown questions concerning MGUS and its relationship with multiple myeloma (MM): Are all myelomas preceded by an MGUS state? What are the evolution patterns of the serum M-proteins and/or FLC prior to the onset of MM? How do the genetic abnormalities progress over time from MGUS to MM in the same patient? Which mechanisms maintain the plasma cell clone in a stable MGUS state and which trigger the progression to MM?<sup>5</sup>

In this issue of *Blood*, Landgren and colleagues report that among 77 476 healthy adults enrolled in a prospective Cancer

Screening Trial, 71 individuals developed MM.<sup>7</sup> In all patients, there were stored serum samples obtained from 2 to 10 years prior to the diagnosis of MM. Serum protein electrophoresis, immunofixation, and kappa-lambda serum FLC assays were performed to determine the prevalence of MGUS and to longitudinally characterize the evolution patterns of the M-proteins prior to the diagnosis of MM. All of the 71 patients who had developed MM had a preceding MGUS, with 75% of them having a detectable M-protein 8 or more years prior to the diagnosis of MM. Interestingly, in about half of the patients, the serum M-protein and the involved FLC showed a year-by-year increase prior to the diagnosis of myeloma. Weiss and colleagues also report on the prevalence of MGUS in 30 patients with MM in whom there was available serum stored by the US Department of Defense Serum Repository.<sup>8</sup> These sera were obtained during the mandatory blood tests performed on active US military service members and were collected 2 to 15 years prior to the MM diagnosis. A preceding monoclonal gammopathy was detected in 90% of the patients (27 of the 30). The authors also studied the serial changes in the levels of serum M-proteins and FLC prior to the diagnosis of MM and found that in 7 of 10 patients with sufficient longitudinal available samples, there was a progressive increase in the FLC ratio, with or without a corresponding change in the intact immunoglobulin level prior to the diagnosis of MM.

These articles answer 2 important questions about MGUS. First, virtually all cases of MM are preceded by MGUS. Second,

the evolution patterns of M-protein/FLC before the development of MM have been characterized: 30% to 50% had a stable MGUS state until MM developed while 50% to 70% of the patients showed a gradual and progressive increase in the M-protein and/or involved FLC. The latter pattern likely corresponds with the so-called evolving MGUS, first recognized by our group.<sup>6</sup> In fact, it can be speculated that all the “evolving” MGUS are slowly growing myelomas from the beginning.<sup>6,7</sup> While the recognition that all myelomas are preceded by MGUS is an important step forward, we do not yet know the precise mechanisms that maintain the MGUS state and the mechanisms that trigger progression from MGUS to MM. Further work should be focused on a better understanding of the molecular basis of the disease. It is hoped that this will result in the identification of novel molecular targets involved in the progression from MGUS to MM and in the development of targeted therapies for patients with MGUS, particularly for those at high risk of progression. This could also result in restoring the MGUS state in patients who have already evolved to MM.

*Conflict-of-interest disclosure:* The authors declare no competing financial interests. ■

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