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estimates based on direct emission measurements, and lower than estimates based on the models used for local environments, but that are still within the range of uncertainty[6,7]. A promising approach for developing global maps of isoprene emissions is to make satellite observations of isoprene-oxidation products[8], but this requires an accurate understanding of isoprene-oxidation processes.

The inability of ACMs to incorporate measured isoprene emission rates is not limited to simulations of the undisturbed tropics. Air-quality modellers at US regulatory agencies have also had to decide between using isoprene emission rates based on measurements, or using inaccurate, substantially reduced emission rates that improve the ability of their model to simulate the actual distribution of oxidants[9]. Those modellers opted for the second approach. This might mean that they get the right answers for the wrong reason, but with pressing deadlines for regulatory decisions, they don't have time to wait for scientists to thrash out all the necessary details. Nevertheless, Lelieveld and colleagues' findings[1] should stimulate a re-evaluation of current predictive methods, in which the accuracies of the individual components of an ACM are considered afresh.

None of the recent field campaigns[1,3,4] that looked at isoprene oxidation over remote tropical forests has quantified all of the variables required to adequately constrain model simulations. Lelieveld and colleagues' measurements of •OH concentration are an invaluable step in the right direction, but simultaneous studies of •OH and isoprene fluxes, and of a more comprehensive suite of radicals and isoprene-oxidation products, are also needed. And as the authors point out, laboratory studies of isoprene-oxidation pathways will be essential to understand the processes maintaining •OH levels over tropical forests.

Field studies in less pristine regions are also required to determine whether such oxidation processes are relevant outside Earth's few remaining unpolluted locations. This could lead to a better understanding of the effect of air-quality degradation on the chemical interactions between the biosphere and the atmosphere, and perhaps strengthen arguments for controlling emissions of atmospheric pollutants. ■

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IMMUNOLOGY

Blood lines redrawn

Thomas Graf

The generation of blood cells is a complex affair. As the culmination of several years of study by various investigators, the latest research will necessitate revision of textbook accounts of the process.

Red cells, white cells and platelets — on the face of it, the main components of blood look simple enough. All of them are ultimately produced from a common source, haematopoietic stem cells. And the white cells, or leukocytes, have a common general function, that of immune defence. But compared with red cells and platelets, leukocytes come in a large variety of specialized types, produced by a still somewhat mysterious variety of intermediate progenitor cells.

On pages 764 and 768 of this issue, Bell and Bhandoola[1] and Wada *et al.*[2] provide definitive evidence that a central aspect of blood-cell differentiation requires a rethink. Taken together with preceding work, their results show that a previously well-recognized distinction between two developmental lineages — lymphoid and myeloid — does not apply. But to appreciate this news, more details about each of the players and their function are required.

Immune cells are devoted to innate or to adaptive immunity. Components of the innate immune system are natural killer (NK) cells, monocytes/macrophages, granulocytes (a classification that includes neutrophils, eosinophils and basophils), mast cells and dendritic cells. The two arms of adaptive immunity are antibody-producing B cells and two types of T cell, cytotoxic and helper, which are respectively characterized by CD8 and CD4 cell-surface proteins. The well-established thinking has been that, along with NK cells, B and T cells are products of the lymphoid haematopoietic lineage, with all the others — including red cells and platelets — forming from the myeloid lineage. Most blood-cell production occurs in the bone marrow, with the exception of T cells, which originate in the bone marrow but mature in the thymus, a small organ in the upper chest.

The basis for the well-established picture stems from 1997, when a common lymphoid progenitor (CLP) was described[3]; this progenitor could give rise to B and T cells as well as NK cells, but not to the myeloid lineage. A few years later the same investigators identified[4] a common myeloid progenitor (CMP), resulting in a haematopoietic tree that symmetrically branches into lymphoid and myeloid cells; this became the classic scheme of haematopoietic differentiation (Fig. 1). A prediction of this scheme was that CLPs migrate from the bone marrow to the thymus to initiate T-cell development. But this concept was subsequently challenged when it was reported that the predominant thymus-seeding cells do not resemble CLPs but have the characteristics of earlier haematopoietic progenitors[5].

T-cell development in the thymus is astonishingly complex, occurring in up to nine sequential stages[6] that are identified by differences in gene expression and developmental potential. The stages can be simplified into the following succession: early T-cell progenitors (ETP, also called double-negative 1, or DN1, cells); DN2 and DN3 cells; CD4/CD8 double-positive cells; and finally CD4 or CD8 single-positive T cells. The various stages are orchestrated by the different microenvironments to which the cells become exposed as they migrate through the thymus[7].

At which stage do thymic T-cell precursors lose their capacity to differentiate into alternative cell types? In line with the CLP model, mice in which the powerful T-cell regulator Notch1 was inhibited showed an increase in the number of thymic B cells but apparently not of myeloid cells (reviewed in refs 6 and 8). Against the model were several reports showing

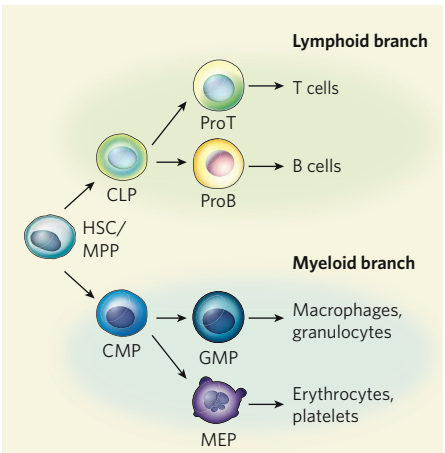

Figure 1 | Classic scheme of haematopoiesis with an early bifurcation into lymphoid and myeloid branches. HSC/MPP, haematopoietic stem cell/multipotent progenitor; CLP, common lymphoid progenitor; CMP, common myeloid progenitor. ProT and ProB are progenitor cells that go through several stages to eventually produce T and B cells. GMP, granulocyte macrophage progenitor; MEP, megakaryocyte erythroid progenitor, which gives rise to erythrocytes (red blood cells) and platelets. T cells are specified in the thymus; all other lineages originate in the bone marrow. Arrows indicate cell differentiation.

that the earliest T-cell progenitors have the potential to become macrophages and dendritic cells (reviewed in refs 6, 9 and 10). However, as these experiments were not done clonally under conditions that permit both lymphoid- and myeloid-cell development, the existence of bipotent T-cell/myeloid precursors had not been demonstrated. And even if such progenitors existed, it remained unclear whether they actually participate in the generation of both mature T cells and myeloid cells in the thymus.

Using single-cell assays, Bell and Bhandoola[1] and Wada *et al.*[2] now demonstrate that ETP/DN1 as well as DN2 cells lack B-cell potential, and that a substantial proportion of them have both T-cell and myeloid potential; the latter capacity is lost from the DN3 stage onwards. The myeloid cells in the T-cell/myeloid colonies were found to be predominantly macrophages, but granulocytes[1], dendritic and NK cells[2] were also evident. Intrathymic transplantation experiments[2] of DN1 cells into T-cell-deficient mice showed that about a third of the macrophages were derived from T-cell progenitors; they were detectable in the cortex of the thymus, corresponding to the normal location of thymic macrophages.

In addition, myeloid cells that were purified from the thymus exhibited rearrangements of the genes encoding the business part of the T cell, the T-cell receptor, which are characteristic of ETP/DN1 cells. Finally, a substantial proportion of thymic granulocytes could be lineage-traced[1] to cells that exhibit a particular enzyme activity. The enzyme concerned, RAG recombinase, is central to creating T-cell-receptor diversity, indicating that this myeloid-cell population originates from ETP/DN1 cells in animals.

The new findings leave little room for a physiologically relevant, lymphoid-restricted T-cell progenitor, and call for a revised thymic lineage tree that has a lymphoid–myeloid branching point (Fig. 2). This type of branching seems to be conserved during development, as T-cell/myeloid but not T-cell/B-cell progenitors were found in the fetal liver[2,11]. The existence of lymphoid–myeloid progenitors might also explain the existence of acute myeloid leukaemias that show T-cell-receptor rearrangements. Finally, the revised picture is supported by the remarkable ease with which committed T-cell progenitors can be redirected to become macrophages and dendritic cells using myeloid gene transcription factors[12].

The observation that many T-cell/myeloid progenitors retain dendritic, NK and granulocytic potential raises the question of whether the earliest lineage decisions occur in a sequential fashion or at random. In support of the first possibility is the finding that two subsets of DN2 cells can be distinguished using lineage-tracing experiments, one with and another without the potential to differentiate into dendritic cells[13]. But it is unclear whether subpopulations exist that are restricted in their NK and granulocytic potential.

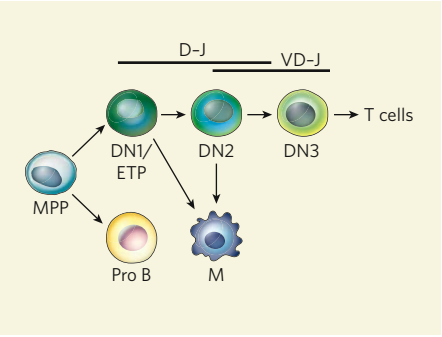

Figure 2 | Revised scheme for thymic T-cell differentiation. The notable difference from Fig. 1 is loss of B-lineage potential before loss of myeloid potential. ETP, early T-cell progenitor, or DN1. DN1 and DN2 are stages of cell differentiation that are subsumed within the ProT category in Fig. 1; DN3 cells belong to a 'PreT' category. The thymus-seeding cells (here designated as MPP) come from the bone marrow through the circulation. Their nature is controversial, and they probably consist of various progenitor subpopulations[5,14,15]. The frequency of transition into macrophages (M) declines from the DN1/ETP stage to the DN2 stage and is lost at the DN3 stage, the T-lineage commitment point. DN1/ETP and DN2 cells have additional differentiation potentials not represented here. The bars underlying D–J and VD–J indicate the rearrangement of T-cell-receptor β-chains and their timing during differentiation.

Developmental immunology has derived great impetus from the simplicity and elegance of a haematopoietic lineage tree symmetrically divided into lymphoid and myeloid branches. But reality is evidently not so neat. The broad lesson to be learned from the revised tree is that it is not always possible to extrapolate from a progenitor's potential to its actual role *in vivo*. A challenge for the future, therefore, is to establish lineage trees that faithfully represent the predominant developmental flows *in vivo*, both in qualitative and quantitative terms. Getting lineage relationships right is essential for successfully modelling the changes in the networks of transcription factors and molecular landscapes that occur as precursors differentiate into mature cells. Bell and Bhandoola[1] and Wada *et al.*[2] have brought T-cell development a step closer to becoming one of the premier systems in which this goal may be achieved. ■

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MATERIALS SCIENCE

Strong teeth, strong seeds

Peter Ungar

A full account of the relationships between tooth form, structure and function remains out of reach. Viewing teeth from an engineering materials perspective offers a way to help crack the problem.

Thickened tooth enamel is a trait that separates most early hominins (our distant ancestors and cousins) from the chimpanzees and gorillas (our nearest living relatives). According to conventional wisdom, our forebears came out of the trees as the savannahs spread through eastern and southern Africa between about 2.5 million and 1.5 million years ago. The story goes that this change of venue was accompanied by a change in diet from soft, fleshy forest fruits to hard, brittle roots, tubers or other savannah foods. An open setting also meant more grit and an increasingly abrasive diet. Thus, enamel that was thickened to resist breakage and wear is seen as a milestone on the road to humanity. Although relationships between tooth-crown height and habitat type have been proposed for some mammals[1], and associations between enamel thickness and food hardness have been documented for others[2], there is no overarching body of theory to explain the evolution of this trait.

Writing in *BioEssays*, Lucas *et al.*[3] address this problem in mammalian evolution from the perspective of engineering materials science. They use the principles of fracture and deformation mechanics to predict the thickness and distribution of enamel on the crowns of