The hemangioblast: a state of competence

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In this issue of Blood, Myers and Krieg present an elegant series of experiments, which suggest that the hemangioblast may be a state of competence rather than a bipotential progenitor state that exists in vivo.1

In the 1930s, following the careful observations of Murray in chick embryos and those of Sabin 2 decades earlier, Murray postulated that blood and endothelial lineages may share a common progenitor: the hemangioblast.2,3 Over the years, evidence has steadily accumulated in support of the hemangioblast. However, these confirmatory studies have been largely based on experiments that relied on the isolation, culture, and/or manipulation of cells in vitro.4-6 A recurring question has remained as to whether hemangioblasts actually exist at all, and thus it provides a convenient model system to tackle this question. Previously, it had already been shown that cells in the VBI of frog embryos express both hematopoietic and endothelial markers, consistent with the putative hemangioblasts. However, the question had remained unresolved as to whether these cells represented bona fide hemangioblasts in vivo. To answer this question, they performed a series of experiments aimed at finally putting this issue to rest. First, they removed the VBI from early embryos and asked whether embryos lacking a VBI would go on to express both primitive blood and endothelial markers at later stages? The answer was that removal of the VBI resulted in a clear loss of primitive blood lineages, but the endothelial lineages remained intact. This finding suggested that the VBI is not a major source of endothelial cells in the early embryo. However, these findings did not exclude the possibility that some endothelial lineages may still arise from the VBI, albeit in smaller numbers. Thus, Myers and Krieg performed a series of classic specification assays. They isolated and cultured the VBI as explants, to ask whether this tissue could form both lineages when cultured in isolation? The answer was that the isolated VBI explants could only give rise to blood but not endothelial lineages. These results suggested that the VBI is specified only to give rise to blood cells. Finally Myers and Krieg performed a further set of fate mapping studies, using homotopic transplants, to ask whether the normal fate of the VBI was to give rise to both blood and endothelial lineages, or only blood, as suggested by their specification mapping studies. The results from these experiments showed that the VBI will normally only give rise to blood lineages and not endothelial lineages in vivo. Thus, they concluded that the VBI in early frog embryos does not contain bipotential precursor cells that give rise to both blood and endothelial lineages, and thus, that the this region does not contain what has been classically defined as hemangioblasts in vivo.

Myers and Krieg, however, performed a further series of experiments, which were especially revealing and may explain what the hemangioblast represents in developmental terms. The authors executed several experiments aimed at disrupting growth factor signaling or the erythroid specification program in the VBI and then assessed how these manipulations affected the development of blood vs endothelial lineages within the VBI. These experiments showed that inhibiting bone morphogenetic protein signaling or disrupting the erythroid program in the VBI largely eliminated red blood cells while allowing a preponderance of endothelial cells to form within this region. Thus, although the VBI is not only specified but also fated to give rise to endothelial cells, the VBI can, under experimental conditions, give rise to endothelial lineages. In other words, the VBI is competent to give rise to both primitive blood cells and endothelial cells, but the latter fate is only revealed under specific experimental conditions whereby either signaling or fate specification is disturbed. The definition of competence in embryology refers to the range of cell fates, which can be achieved by a cell or group of cells, given the appropriate conditions. A cell or tissue may be competent to give rise to many cell types that it would not normally be specified or fated to form. A clear example of this are the animal cap cells from blastula stage frog embryos, which, although they are specified and fated to give rise only to ectodermal tissues, are competent to form virtually any cell type in the embryo, given the appropriate signals.10 The findings from Myers and Krieg suggest that a similar scenario may explain what the

Is the hemangioblast a bipotential precursor state or a bipotential competence state, which reveals its latent developmental potential only under experimental conditions?
hemangioblast is—a state of competence. This might help resolve many of the apparently controversial findings over the years. It is particularly notable that most of the experiments suggesting the existence of a bipotential precursor state for blood and endothelial cells have come from in vitro explant or cell culture studies, where the experimental manipulations may have been uncovering a latent competence state rather than an inherent precursor state.

If the hemangioblast is a state of competence, rather than a bona fide bipotential precursor state, should this affect their potential use in developmental biology or regenerative medicine? The short answer is no. These cells can still be used to help decipher the molecular mechanisms that drive both lineages, as well as how one developmental program might impact on the other. Furthermore, whether the hemangioblast is a state of competence or an actual precursor state should not have a significant impact on how these cells could be exploited to generate or expand either lineage for regenerative medicine purposes. Perhaps the greatest implication of these studies is that it may help explain some of the controversies that have confounded this field in recent years.

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LYMPHOID NEOPLASIA

Comment on Abrisqueta et al, page 3951

Maintenance in CLL

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In this issue of Blood, Abrisqueta and colleagues report on the outcomes of a phase 2 clinical trial evaluating rituximab maintenance therapy in chronic lymphocytic leukemia (CLL) patients after treatment with rituximab, fludarabine, cyclophosphamide, and mitoxantrone (R-FCM).1

Despite significant progress, CLL remains an incurable disease and the introduction of new drugs and new therapeutic strategies is still awaited. Consolidation and maintenance therapy is a promising concept that can further improve response quality and duration in CLL patients. In indolent non-Hodgkin lymphoma patients, particularly in follicular lymphoma, large randomized trials have indicated that rituximab maintenance treatment after induction therapy improves results in previously treated and untreated patients.2,3 In follicular lymphoma, 2 years of rituximab maintenance therapy significantly improves prolonged progression-free survival (PFS) when given after immunochemotherapy as a first-line treatment of induction and is the current standard of care.

The approval of rituximab-based immunochemotherapy can be viewed as a substantial therapeutic advance in CLL. A large phase 3 randomized trial demonstrated that rituximab combined with fludarabine and cyclophosphamide (RFC) increased the overall response and complete response (CR) rates, prolonged PFS and overall survival (OS) as compared with fludarabine and cyclophosphamide in previously untreated patients.4 On the basis of these results, RFC has become the first-line treatment of choice for younger CLL patients.

There has also been some exploration of rituximab as maintenance therapy in CLL.5,6 In these small studies, maintenance therapy with rituximab was successfully conducted for 6 months or longer. Long-term toxicity, based on hematologic and immunologic parameters, was mild. Encouraging results were also seen in a recently published study by Wiernik and Adiga in which patients receiving rituximab maintenance therapy demonstrated a median duration of response substantially longer than those who did not receive maintenance (35 months vs 14 months, respectively).6

In this issue, Abrisqueta et al report a phase 2 clinical trial consisting of an initial treatment with R-FCM followed by rituximab maintenance.1 Sixty-seven patients achieving response after R-FCM received maintenance therapy with 375 mg/m² rituximab every 3 months for 2 years. At the end of the maintenance therapy, 40.6% of patients were in minimal residual disease (MRD)–negative CR, 40.6% were in MRD-positive CR, while 4.8% remained stable in partial response. Importantly, 21% of the patients in CR MRD-positive or in partial response in the end of R-FCM induction therapy improved their response after rituximab maintenance. A 4-year PFS and OS were 69.1% and 90.5% for all patients and 74.8% and 93.7% for patients receiving rituximab maintenance, respectively. These results seem to be better than those reported for RFC therapy from the German CLL Study Group (GCLLSG) CLL8 trial, which concluded with a 65% 3-year PFS and 87% OS. As expected, MRD status after R-FCM therapy was the strongest predictor of PFS. Grade 3/4 neutropenia was observed in 8.5%, and 16 patients experienced grade 3/4 infectious episodes. Maintenance with rituximab after R-FCM improved the quality of the response, particularly in patients who were MRD-positive after initial treatment and who obtained a prolonged PFS. These results are encouraging, but a randomized trial is necessary to establish the possible advantage of such maintenance treatment over standard RFC therapy in previously untreated CLL patients.

We should remember that other agents can also be useful in the maintenance therapy

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