Rac GTPases play multiple roles in erythropoiesis

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their name to legitimize something they cannot really vouch for. Though, more often than not, authors get away with it, authors should be very wary of being guests. In a number of recent high profile cases of fraud some senior authors have protested that they knew nothing about the alleged misconduct, only to have their protestations met with incredulity. It is a forceful reminder that authorship is a responsibility not just a privilege and should be offered or accepted with appropriate consideration.

What can be done?

If there is one lesson to be learned from all these cases of ghost, guests and other illegitimate authors it is that authorship has somehow slipped recently from something to be earned through a specific, meaningful contribution to a superficial designation that can be traded. These slippery notions of authorship have not come out of a vacuum, and were certainly not invented by pharmaceutical companies. The issue of guest authorship – of including the head of department among the list of authors of a paper for no other reason than esteemed status – has been widespread in academia for many years. I would argue that it is this culture that pharmaceutical companies have tapped into, rather than inventing a new type of author. But by flattering academics into being guest authors, they have created, and then filled, a need for ghost authors to actually write the papers. The academics accepting the apparent honor of authorship thus provide cover – as accomplices or as dupes – for manipulative marketing practices.

Some have interpreted the anxiety over ghost authors as a call to remove all medical writers from papers but that is not the case. Medical writers do have a role to play in writing papers, but somehow, as we have argued before, without appropriate standards this legitimate role can be turned into something that subverts and threatens medical publishing more widely.

It is clear then that the responsibility for addressing the mismatch between what an author should be and what authorship has come to mean lies with many groups.

Journals clearly have a role to play in identifying and correcting the most egregious examples. And pharmaceutical companies must accept that trying to hide ghost, or entice guest authors is not acceptable. But the primary responsibility for prevention lies much further back, within the institutions where authors work, and where medical academics are trained. Authorship of a scientific or medical paper must be returned to something that can be a source of pride, and which is deserved and earned – and declared.

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References


Rac GTPases play multiple roles in erythropoiesis

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The four members of the Rac family of GTPases – Rac1, Rac2, Rac3 and RhoG – are members of the Rho superfamily that regulates the organization, dynamics, and function of the actin cytoskeleton. Rac GTPases play significant roles in many cellular processes including migration, cytokinesis, lamellipodia formation, and cell polarity.1 Genetically modified mice deficient in each of the Racs are available,2-4 deficiency of Rac1 causes intrauterine death, whereas mice defective in Rac2, Rac3 or RhoG develop fairly normally. Rac proteins may have redundant functions in certain types of cells and unique functions in others.

As shown by single- and double knock-outs of Rac genes, the Rac GTPases play important roles in many hematopoietic cells.7 Rac2 is specifically expressed in hematopoietic cells, and is directly involved in chemotaxis and superoxide production in neutrophils and macrophages.5,8 In addition, Rac2, together with Rac1, mediates B-cell receptor signaling pathways.12 T-cell activation is also affected in Rac2-deficient mice13 and hematopoietic stem cells from Rac2−/− mice show defective long-term engraftment.14

In contrast, Rac1 is ubiquitously expressed and plays essential roles in several organ systems, including
hematopoietic cells. Using a hematopoietic cell-specific knockout of Rac1, Gu et al. demonstrated that deletion of Rac1 blocks the ability of hematopoietic stem cells to engraft irradiated recipient mice. When crossed with Rac2-/- mice, a hematopoietic-specific deletion of Rac1 results in a massive egress of hematopoietic stem cells into the blood from the bone marrow. Rac1 regulates signaling pathways downstream of integrins and c-kit in mast cells and hematopoietic stem cells and presumably these defects cause loss of adhesion of the hematopoietic stem cells to the bone marrow stroma.

**Rac GTPases play essential roles in erythropoiesis**

There is growing evidence that Rac GTPases are essential for erythropoiesis. In this issue of the Journal, Kalfa et al. demonstrate that Rac1 and Rac2 are required for early stages of erythropoiesis in the bone marrow but – surprisingly – not in the spleen. Using hematopoietic tissue-specific Rac1 knock-out mice in a total Rac2-/- background, they showed that deficiency of both Rac1 and Rac2 blocks early stages of erythropoiesis in the bone marrow without affecting cell survival or proliferation. Abnormalities in the morphology of erythroid burst-forming units resembled alterations seen previously in Rac1-/-;Rac2-/- myeloid colonies, and suggested an impairment in cell migration and/or proliferation. These results indicated that Rac1 and Rac2 have redundant but essential roles in the early erythroid progenitor stages of erythropoiesis in the bone marrow.

The same group previously reported that Rac1-/-;Rac2-/- erythrocytes have an unstable cytoskeleton; deficiency of Rac1 and Rac2 alters actin assembly and decreases erythrocyte deformability, and generates a hemolytic anemia. Thus, it was not surprising that in these Rac1-/- Rac2-/- mice there was compensatory erythropoiesis in the spleen. What was surprising was that splenic erythroid progenitors somehow circumvented the deficiency of the Rac1 and Rac2 GTPases.

While Kalfa’s study focused on early stages of erythropoiesis, we showed that Rac1 and Rac2 are required for enucleation of late stage erythroblasts. Deregulation of Rac GTPases during the late stages of erythropoiesis completely blocked enucleation of cultured mouse fetal erythroblasts without affecting their normal proliferation and differentiation. The contractile actin ring that forms on the plasma membrane of late-stage erythroblasts at the boundary between the cytoplasm and nucleus of enucleating cells was disrupted when Rac GTPases were inhibited in late stages of erythropoiesis. This effect of Rac GTPases was mediated by their downstream target mDia2, a formin protein required for nucleation of unbranched actin filaments. This function of Rac GTPases in enucleation is specific to Rac1 and Rac2 since RhoA and Cdc42 are not involved in this process.

The current work by Kalfa et al. is important because it reveals that Rac1 and Rac2 are required during early stages of erythropoiesis as well as for enucleation and the integrity of the red cell cytoskeleton. Like all good papers it raises more interesting questions than it answers. For instance, we do not know whether Rac3 or RhoG play any role in red cell formation or function. Since there are no significant erythropoietic phenotypes in Rac3 and RhoG knock-out mice, it is likely that other Rac GTPases family proteins compensate for any possible negative effects of deletion of these proteins. In this aspect, in vitro studies of cultured mouse erythroblasts could elucidate whether Rac3 and RhoG have functions in erythropoiesis.

Kalfa et al. show that the major disorder of Rac1-/-;Rac2-/- hematopoietic cells is the defective proliferation of myeloid-erythroid progenitor cells in the bone marrow, but there is a normal or possibly increased survival and/or proliferation of these progenitors in the spleen. Presumably, as noted by the authors, this derives from differences in the bone marrow and splenic microenvironment, but we do not know which cytokines or other factors produced by stromal cells may be responsible for this crucial difference. Bone marrow transplantation studies of Rac1-/-;Rac2-/- hematopoietic progenitors into normal recipients, and vice versa, could begin to separate the hematopoietic cell autonomous functions of Rac1 and Rac2 from those of the stromal populations.

We would also like to know how Rac1 and Rac2 regulate differentiation of erythroid progenitors. As discussed by the authors, cytokine-mediated signaling pathways may be involved. In other cell types Rac GTPases regulate gene expression and cell transformation in multiple pathways, such as in the Jun N-terminal kinase and Ras signaling pathways, and these or other pathways could mediate the effects of Rac GTPases in early stages of erythropoiesis.

Dr. Lodish is a Professor of Biology at the Massachusetts Institute of Technology and a member of the Whitehead Institute for Biomedical Research.

**References**

Sickle cell disease: primum non nocere (first do no harm)
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Was Hippocrates aware when he insisted that physicians primum non nocere (first, do no harm) that this precept would still prove challenging to his colleagues 2000 years later? In his day, diseases were probably diagnosed only in the presence of overt symptoms, and asymptomatic children were no doubt considered healthy, as there were no means of predicting the subsequent development of diseases that might decrease their chances of living long and happy lives.

Times have changed, and we are now able to diagnose diseases in asymptomatic children, especially through neonatal screening. In sickle cell disease (SCD), for example, neonatal screening can dramatically improve the prognosis: a 2007 report of an English cohort screened at birth and enrolled in a comprehensive follow-up program showed that children with hemoglobin SS had a 99% chance of living at least 16 years. In addition to a substantial improvement in survival, a marked decrease in morbidity, chiefly due to reductions in stroke, recurrent painful crises and recurrent acute chest syndrome, has been achieved in children with SCD.

A characteristic feature of SCD is the wide variation in clinical expression between patients. To date, only a few factors, either at birth or later on, reliably predict the subsequent development of severe complications. Nevertheless, as a rule, children who experience severe complications early in life continue to express a severe disease phenotype throughout their lives whereas those with mild disease continue to do well, although exceptions may occur.

In recent years, various therapeutic approaches have reduced the risk of stroke, pain and acute chest syndrome in SCD. Transcranial Doppler followed by regular transfusions in children with high cerebral blood flow velocities has decreased the risk of a first stroke by 90%. Hydroxyurea (hydroxycarbamide) very significantly decreases the frequency and severity of vaso-occlusive crises in SCD. Transcranial Doppler followed by regular transfusions also probably diagnosed only in the presence of overt symptoms, and asymptomatic children were no doubt considered healthy, as there were no means of predicting the subsequent development of diseases that might decrease their chances of living long and happy lives.

In recent years, various therapeutic approaches have reduced the risk of stroke, pain and acute chest syndrome in SCD. Transcranial Doppler followed by regular transfusions in children with high cerebral blood flow velocities has decreased the risk of a first stroke by 90%. Hydroxyurea (hydroxycarbamide) very significantly decreases the frequency and severity of vaso-occlusive crises in SCD. Transcranial Doppler followed by regular transfusions also probably decreases the frequency and severity of vaso-occlusive crises in children. However, hydroxyurea and regular transfusion also generate a burden for the patient and family and they fail to completely eliminate the risk of complications such as recurrent stroke or painful events. In addition to the need for daily treatment and fear of uncontrolled complications, SCD usually generates a feeling of being different, misunderstood and inadequate. Families and patients may experience post-traumatic stress disorder, the rate of occurrence of which is not correlated with disease severity.

Thus, the disease itself, independently of the number of hospital admissions and complications, adversely affects the quality of life of the patients and their families. This quality-of-life burden is being increasingly recognized by physicians and families as a key component in the risk/benefit ratio of treatments for SCD.

A case in point is the risk/benefit ratio of hematopoietic stem-cell transplantation (HSCT) for SCD using marrow from an HLA-identical sibling. Studies from a number of groups of patients transplanted between 1988 and 2004 show an overall survival rate of 93-95% and an event-free survival rate of approximately 85-86% after a median follow-up of 5-6 years. The possibility of cure is a major advance for both SCD patients and their families. The