DMS may trigger actin polymerization via the WASp/WAVE pathway.

Reports over the past 5 years have significantly advanced our understanding of the structural and mechanical aspects of proplatelet formation. Schulze and colleagues provide initial insights into the formation and function of the DMS, including its role in platelet biogenesis, furthering our understanding of this most mysterious cell, the megakaryocyte. Dr Wright should be pleased, but I suspect he is wondering what took so long.

**REFERENCES**


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**GENE THERAPY**

Comment on Gangadharan et al, page 3859

# Bringing home the bacon for hemophilia

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Hematopoietic stem cell–directed gene therapy with a retroviral vector expressing the pig FVIII gene cured hemophilia A without inhibitor formation in mice. This approach holds promise for prevention of bleeding or tolerance induction in patients.

Hemophilia A is due to factor VIII (FVIII) deficiency and results in bleeding in 1:5000 males. Although it can be treated with infusions of human FVIII, this costs more than $100 000 per year for patients with less than 1% of normal activity.

A feared complication of human FVIII replacement therapy is the development of inhibitors, which occurs in 25% of patients with severe disease. Inhibitors can be eradicated in 70% of patients with immune tolerance induction, which involves frequent injections of high doses of human FVIII and costs $1 000 000 per year for a child. Although patients with inhibitors are treated effectively with bypass agents such as recombinant factor VIIa, one dose of FVIIa for a 53-kg patient costs $10 464 at our hospital. Total costs for 7 to 10 days of treatment after major surgery or a serious bleed can exceed $500 000. Prevention of inhibitor development would be a major advance.

The paper by Gangadharan and colleagues demonstrates that hematopoietic stem cell (HSC)–directed gene therapy with a retroviral vector expressing porcine FVIII cured hemophilia A mice without inhibitor development (see figure). This result is consistent with that of Moayeri et al who performed HSC transplantation in hemophilia A mice using a retroviral vector expressing the human FVIII gene.

There are 2 major advantages to using the porcine gene. First, the porcine FVIII gene resulted in greater activity in vivo than the human FVIII gene, which is probably due to a higher specific activity of the pig protein. Second, most inhibitors to human FVIII do not cross-react with porcine FVIII, making it possible that a vector with the porcine gene might be used in the large subset of patients that already has inhibitors to human FVIII. Although plasma-derived porcine FVIII is not currently available, recombinant porcine FVIII is being tested.

There are also caveats. First, use of this gene required at least partial bone marrow ablation, which has toxicities, and would be difficult to justify for patients with hemophilia. However, an in vivo delivery of retroviral vector to HSCs could have a similar effect. Indeed, neonatal intravenous injection of a retroviral vector expressing canine FVIII cured hemophilia A dogs without inhibitor formation. Since this procedure transduces HSCs in addition to liver cells, it is possible that the tolerance to canine FVIII was due to the transduction of blood cells. An in vivo delivery without selection should be clinically acceptable if it were safe. However, the second caveat of using HSC-directed gene therapy in patients is that an integrating retroviral vector might result in leukemia due to insertional mutagenesis. It will be important to demonstrate that this risk is very low. Nevertheless, the paper by Gangadharan et al suggests that a cure may be on the horizon for hemophilia A.

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