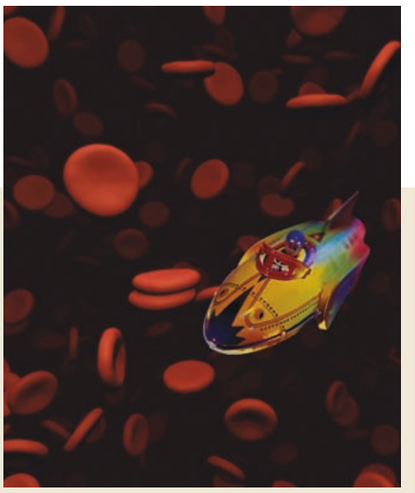
DRUG DELIVERY

Blood vessel

In many ways, erythrocytes would make an ideal agent for drug delivery. They are the most abundant cellular constituent in blood, and on average travel hundreds of kilometres in the vasculature during their lifespan (100–120 days). If they could be converted into carriers, they could, in theory, prolong the circulation and improve the bioavailability of drugs that act in the bloodstream. Loading therapeutic agents into erythrocytes is of limited value, as many drugs diffuse poorly across the erythrocyte membrane. However, coupling agents to the erythrocyte surface could overcome this problem. Now, Muzykantov and colleagues provide the first proof of principle for this drug delivery strategy in *Nature Biotechnology* by showing that this can improve the therapeutic profile of tissue plasminogen activator (tPA) in prophylaxis of vascular thrombosis (a blood clot that develops in an artery and remains in place).

Existing treatments that lyse clots (fibrinolysis), such as tPA, are good for treating acute post-thrombotic ischaemic events, such as myocardial infarction, but are unsuitable for prophylaxis because they have a short lifespan, dissolve both pre-existing and nascent clots (ideally, nascent clots should be selectively targeted), and leak out of the vasculature and cause side effects in other tissues. But biotinylating tPA and erythrocytes, and crosslinking them using streptavidin, produces a stable complex that is a potent thrombo-prophylactic agent in animal models of venous and arterial thrombosis. The erythrocyte–tPA complex extended the duration of tPA's fibrinolytic activity and was ten times more selective in lysing nascent over pre-existing pulmonary emboli (blood clots that break off, travel through the bloodstream and stick in a pulmonary artery) than free tPA, and twenty times more selective in lysing nascent over pre-existing arterial clots. Prophylactic injection of erythrocyte–tPA dissolved occlusive thrombi in the carotid artery soon after their formation, even though they were resistant to fibrinolysis by free tPA injected before or after thrombosis.

The authors say that the strategy works because the coupled tPA is denied access to the relatively impermeable preformed clots and extravascular tissues, thereby reducing the risk of bleeding. The complex circulates for prolonged periods and becomes incorporated inside nascent clots, initiating lysis from within (which they call "the 'Trojan horse' fibrinolysis of nascent clots"). Proving that the method works in other preclinical and clinical models will be important, but a more interesting question will be the wider one of how many other agents can have their therapeutic profiles enhanced by coupling to erythrocytes.



Simon Frantz

References and links

ORIGINAL RESEARCH PAPER Murciano, J.-C. *et al.* Prophylactic fibrinolysis through selective dissolution of nascent clots by tPA-carrying erythrocyes. *Nature Biotechnol.* **21**, 891–896 (2003)

DIABETES

Ramping up kinase restores the balance

Mutations of the gene that encodes glucokinase have been previously linked to an autosomal dominant form of diabetes mellitus, maturity-onset diabetes of the young type 2 (MODY2).

In MODY2 patients, loss-of-function mutations decrease the rate at which glucokinase phosphorylates glucose in pancreatic β-cells and hepatocytes. On the basis of these data, Grimsby *et al.* proposed that upregulating glucokinase activity might clinically benefit sufferers of type 2 diabetes. As such, they set out to find activators of this key homeostatic enzyme.

A screen of 120,000 structurally diverse synthetic compounds identified one small molecule that enhanced the activity of glucokinase. Chemical optimization produced a racemic mixture, the *R* enantiomer of which — RO-28-1675 — potently activated recombinant human glucokinase in a dose-dependent manner. This enhanced activity was a function of an increase in the maximal velocity of the enzyme, in combination with an increased affinity for its glucose substrate. These effects of RO-28-1675 were specific for glucokinase — the activity of hexokinase isozymes of brain and muscle was not enhanced in its presence.

In isolated rat pancreatic islets, the threshold concentration of glucose required to induce the release of insulin progressively decreased in the presence of increasing concentrations of RO-28-1675. *In vivo*, a single oral dose of RO-28-1675 reduced blood glucose levels in wild-type mice, and in both rat and mouse models of type 2 diabetes. This glucose-lowering effect was accompanied by increasing plasma insulin levels.

The authors showed that in addition to modulating pancreatic function, RO-28-1675 increases the rate at which glucose is utilized in the liver. This dual mechanism of action targeting two of the hallmarks of diabetes — impaired insulin secretion and enhanced hepatic glucose production — is a highly favourable feature of potential therapeutics. If, as the authors suggest, the results of these animal studies with RO-28-1675 can be reproduced in human trials, safe and effective new treatments for diabetes based on activation of glucokinase might make it to the end of the drug development pipeline.

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References and links

ORIGINAL RESEARCH PAPER Grimsby, J. *et al.* Allosteric activators of glucokinase: potential role in diabetes therapy. *Science* **301**, 370–373 (2003)

WEB SITE

Encyclopedia of Life Sciences: http://www.els.net/
Insulin action: molecular basis of diabetes