Targeting drugs to circulating red blood cells

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Technology description

Problem

Annual incidence of venous thrombosis in the U.S. is 1 to 2 per 1000 adults. Roughly 33% of those presenting with a thrombotic event will have recurrence within 10 years. Thrombosis can cause tissue ischemia and damage leading to severe complications and possible mortality.

Conditions associated with uncontrolled acute inflammation such as in adult respiratory distress syndrome (ARDS) are also difficult to manage and have 30-40% mortality, high morbidity and no effective therapy. The pathogenesis is complex and mediated by many factors, including release of cytokines and other pathological mediators, as well as unleashed pro-inflammatory effects of thrombin, i.e., the key agent provocateur of thrombosis.

In both, thrombosis and ARDS-types of inflammation an effective prophylactic or therapeutic agent should act within the blood vessels and avoid aggravating side effects, as patients with these conditions are very fragile. Unfortunately, most drugs on the market freely diffuse throughout the blood stream where they are either taken up by the liver, filtered out by the renal system, or diffuse through the vascular wall, reducing the drug’ s effectiveness. Clinicians must be careful with how much drug they administer, as the excessive diffusion of antithrombotic agents has considerable risk of bleeding and can lead to cerebral hemorrhage and brain toxicity, preventing their use in many patients. The efficacy of anti-inflammatory agents that counter thrombin-mediated inflammatory pathways are limited by the same, and many other, contraindications.

Solution

Dr. Vladimir Muzykantov and his team at Penn Medicine have developed a technology capable of targeting therapeutics to circulating red blood cells (RBCs), thereby avoiding the downsides common to current untargeted therapies. Briefly, Dr. Muzykantov’ s team developed a series of recombinant fusion proteins, coupling an anti-thrombotic agent, anti-inflammatory agent, or a pro-drug with a single chain antigen-binding fragment (scFv) of a monoclonal antibody which binds to an antigen present on the surface of circulating RBCs. This recombinant format allows for the design of small, homologous, quality controlled, and easy to inject fusion proteins that can carry diverse drugs (such as the anti-thrombotic agent tPA or the anti-thrombotic and anti-inflammatory agent thrombomodulin) and target directly to RBCs.

Application area

Thrombosis, scFv fusion protein, anti-thrombotic drug, red blood cell

Advantages

•Rapid, and targeted, binding of the drug to circulating RBCs without altering its biocompatibility
•Drastically prolongs half-life of the drug through the blood cell-bound complex
Limits drug penetration into the blood vessel or surrounding tissues and minimizes adverse side effects
•Unique features of local activation in the site of pathology allowing for enhanced specificity
•Used as a prophylactic given more favorable pharmacokinetics and enhanced sensitivity
•Anti-inlfammatory effects (either prophylactic or therapeutic) are superior vs the same agents that do not bind to RBC

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