Targeted Drug Delivery through Optical Control of Cell Lysis

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Light-induced lysis of red blood cell carriers provides a delivery strategy for protein therapeutics with spatiotemporal control.

The use of red blood cells (RBCs) as natural carriers for the delivery of drugs and therapeutic proteins has gained significant attention in recent years and has entered clinical evaluation. As notably robust delivery systems, RBC carriers can be loaded with the desired cargo by internal encapsulation or through chemical attachment to the cell surface. While both methods permit a prolonged therapeutic effect due to an extended, gradual cargo release as well as protection from immune response and serum proteases, the sustained drug activity can lead to unwanted systemic toxicity. Until now, strategies for controlled, localized therapeutic release from RBC delivery systems have remained elusive. Herein, Lawrence and co-workers engineered a light-responsive RBC-based delivery system for the targeted release of protein therapeutics. Optically controlled drug release has the potential for targeted delivery to disease sites, thereby improving the therapeutic window while concurrently diminishing the chance for off target effects.

Their design employs two lipid (C_{18})-modified peptides, including melittin (Mel), a 26-residue hemolytic peptide, and an inhibitory Mel-blocking peptide, attached to the RBC carrier by embedding them in the lipid membrane. Building upon clever photochemistry previously developed in their lab, the authors generated a photohemolytic trigger by coordinating the inhibitory peptide to the cobalt center of cobalamin, also known as vitamin B12 (Figure 1A). In the absence of light, the hemolytic activity of Mel is masked by the inhibitory peptide, and the protein cargo is retained within the RBCs. Irradiation at 525 nm results in the photo-release of the inhibitory peptide from the B12 cobalt center, which induces Mel activity and self-hemolysis of the RBC carrier and results in the release of the internal cargo (Figure 1B).

The drug delivery system described above cleverly expands upon the B12-based phototherapeutic strategies previously established by the Lawrence group. Distinct from most photocaging strategies, which require the presence of heteroatoms for caging group installation, the cobalamin motif can accommodate alkyl bonds to the cobalt metal center. Because of the relative weakness of this bond, photorelease of the attached alkyl compounds can be achieved with high quantum yield following irradiation with light at a wavelength (330–560 nm) that is absorbed by the corrin ring system (Figure 1A). Further modification with “antennas”, for example, a Cy5 fluorophore, allows for efficient decaging with light capable of deep tissue penetration (600–900 nm), which is difficult to achieve with traditional caging groups that commonly photolyze C–O bonds. While the work highlighted here demonstrates the release of encapsulated protein-based cargos from RBCs, B12 derivatives have also been successfully utilized in wavelength-selective release of various small molecule drugs, including doxorubicin, methotrexate, colchicine, and dexamethasone, from the corresponding

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lipidated B12- and fluorophore-conjugates on the surface of RBC vehicles.4

Using their light-responsive hemolysis delivery system, the authors demonstrate that the extent of fluorescent protein release from the modified RBC carriers directly correlates with light intensity and they showcase tunability of activation as an additional element for control. For practical applications of this system in deeper tissues, the authors functionalized B12 with Cy5, a far-red-shifted fluorophore, to generate a wavelength-specific trigger. Illumination with 660 nm light led to cargo release only in engineered RBCs containing the Cy5 modification, while RBCs surface-loaded with unmodified B12 showed only a minimal response. Thus, appending fluorophores with unique spectral properties accommodates the potential for multiwavelength release of distinct cargos, thereby adding to the optochemical toolbox of regulating different biological processes with different light inputs.6,7

The ability of controlled drug release on command builds onto existing advantages of RBC-based delivery systems, including biocompatibility, prolonged systemic circulation (up to 120 days), and large loading capacity.8 Lawrence and co-workers demonstrate the utility of their system in the controlled release of therapeutically relevant proteins, specifically vascular endothelial growth factor-A (VEGF) and thrombin. VEGF, a key contender for the treatment of cardiovascular diseases, remains a perfect candidate for RBC encapsulation due to its short half-life under physiological conditions, which hinders its overall therapeutic efficacy. Light-mediated release of functional VEGF was detected
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The broad utility of this system lies within the versatility of the hemolytic peptide, which can also be applied for light-induced lysis of other lipid-membrane based carriers.1 Thus, the approach developed by Lawrence and co-workers can most likely be adapted for other carrier molecules including exosomes, microvesicles, and biomimetic nanoparticles. The advantages of RBCs as drug carriers coupled with the diversity of protein cargos that can be accommodated and selectively released using this system offer a unique pathway to addressing many of the challenges associated with protein-based therapeutics and drug delivery systems alike. The tunable, temporal, and spatial control inherent to light-responsive therapeutics is cleverly applied here as an attractive advantage over the long-term sustained release achieved with current RBC systems.9 Future applications of this engineered RBC drug delivery system will most certainly provide novel opportunities as patient-centered and cell-based therapies for precise treatment of localized diseases. Additionally, expansion of this engineered RBC drug delivery platform to other conditional triggers (e.g., biomolecule-sensing10) offers opportunities to reach tissues and organs that are not easily irradiated.

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Notes
The authors declare no competing financial interest.

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