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Cover story

Megakaryocytic microparticles for targeted delivery to hematopoietic stem cells

Selective drug delivery to hematopoietic stem and progenitor cells (HSPCs) is a long-standing challenge of "formidable promise…that may transform medical practice" [1]. Developing vectors that would enable *in vivo* cargo delivery to and manipulation of HSPCs has been a central goal in cell and gene therapy. Drug delivery systems, such as liposomes and nanoparticles, have been assumed to be useful for their increased stability and extended circulation time in blood as compared with soluble therapeutic molecules. Yet, *in vivo* studies have shown that they do not deliver cargo with the desirable efficiency and specificity for the target cells, and new approaches are necessary to overcome this difficulty [2]. To effectively target HSPCs, therapeutic delivery systems must enter the bone marrow, specifically recognize HSPCs and deliver cargo to the cells. This has proven to be notoriously difficult and efforts so far have not resulted in clinically relevant efficiency.

The extracellular vesicles (EVs) may provide a hope. EVs are shed by all cell types of the animal body under various stimulation or stress. EVs come in two different size distributions that result from their different ontogeny. The larger microparticles (MPs; or microvesicles) are 100-1000 nm EVs that carry RNAs, proteins, and phospholipids sorted from their parent cells during MP generation, as they bud off the cytoplasmic membrane of the parent cells. MPs are distinct from the smaller 40-100 nm exosomes, which originate from multivesicular bodies through exocytosis. Over the last few years, EVs have emerged as important mediators of intercellular communication regulating an ever-expanding range of biological processes, both on normo- and patho-physiology. The former include enhancing/accelerating native developmental programs in immunology, vascular repair and angiogenesis, while the latter include important roles in carcinogenesis and cancer metastasis, neurodegenerative disorders, and infectious and cardiovascular diseases. EVs frequently exhibit cell- or tissue-specific tropism, and they can inherently interact with target cells through signaling to deliver cargo via endocytotic processes and cell fusion. These properties make EVs an effective drug delivery system.

The paper by Papoutsakis and collaborators [3] in this issue makes the case for megakaryocytic MPs (MkMPs) as vectors to deliver cargo to HSPCs with great specificity and efficacy. In an earlier study [4], they identified a biological function of MkMPs, namely to enable megakaryocytic differentiation and maturation of HSPCs in the absence of thrombopoietin. MkMPs are the most abundant MPs in circulation, and are biologically inert. The authors show that MkMPs target specifically all HSPCs, and notably the most primitive, lineage-negative HSPCs, which are viewed as the prime target for gene therapy based on their ability to enable long-term reconstitution of the hematopoietic system. Here, they explore the mechanisms by which MkMPs recognize and deliver cargo to HSPCs. They show that both an endocytosis-related mechanism, and membrane fusion are engaged in cargo delivery, and the cargo that enables HSPC fate alteration includes RNAs, most likely small RNAs. For the first time, they provide direct visual evidence via TEM analysis of the multistep process of how MkMPs fuse into the membranes of HSPCs cells.

The study by the Papoutsakis group is important in many ways. The work provides a specific mechanism of cargo delivery which affects the fate of the cargo in the cells. Since direct fusion avoids trafficking nucleic acid cargo through endosomes, it can be exploited to yield potent gene delivery. They also present mechanistic studies to identify the surface receptors that are engaged in target recognition, and show that the HSPC uropods are an important entry point. They demonstrate that cargo delivery depends on processes more complex than receptor recognition. More importantly, instead of trying to find applications of MkMPs, the authors decided to first understand how MkMPs recognize, target and deliver cargo to various HSPCs to alter their fate. Understanding the properties of MkMPs allows engineering of MkMPs to carry exogenous molecules for delivery to HSPCs, and/or identify key surface molecules that mediate the recognition of HSPCs.

It is true that much more remains to be understood: the factors determining MkMP endocytosis or membrane fusion by a HSPC, the specific MkMPs components enabling cargo delivery to HSPCS, the reasons causing the failure of PMPs, the way that MkMPs unload their native RNA cargo, and the method of loading MkMPs with desirable synthetic cargo. These important questions can be answered by the mechanism-first approach taken by the authors. Fundamental understanding of the underlying mechanisms allows rational, step-by-step engineering of the system to improve the MkMP-based delivery system for successful clinical applications. The work by the Papoutsakis team sets the foundation not only for exploiting MkMPs for gene and other cargo delivery to HSPCs, but also for other targeted drug delivery systems. The mechanism-first approach, which has become a rarity nowadays, by the Papoutsakis team, serves as a model for others to follow.

References

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