An EVolving approach to directed enzyme prodrug therapy for cancer

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Abstract

Gene-directed enzyme prodrug therapy for cancer is made more specific via targeted extracellular vesicle-mediated mRNA delivery.

The sci-fi thriller *I, Robot* tells the story of robots attempting to take over the world based on their interpretation of the three governing laws of their programming. This plan is thwarted with the help of Sonny, a unique robot who can ignore the three laws due to being programmed differently. This movie illustrates how selective programming can be a powerful tool that can be used to turn a subset of a population against the rest.
same concept underlies the strategy of gene-directed enzyme prodrug therapy (GDEPT) for cancer, which involves specific delivery of a gene to cancer cells that allows for subsequent activation of a systemically administered prodrug into a toxic form only in cells where an enzyme encoded by the delivered gene is present. Several GDEPT strategies have advanced to clinical trials; however, the specificity and fidelity of gene delivery are still limiting factors to successful translation.

Toward addressing these limitations, Wang et al. describe the use of modified extracellular vesicles (EVs) for targeted delivery of mRNA to cancer cells overexpressing the HER2 receptor. EVs are nanoscale vesicles secreted by many cell types that have been co-opted for a variety of therapeutic applications. However, targeted delivery using EVs has been challenging, as has encapsulation of large nucleic acid cargo. To address cargo encapsulation, the authors applied a transfection-based approach to successfully load exogenous mRNA encoding for the enzyme HChrR6 into EVs. To address targeting, the authors created a novel chimeric protein consisting of a HER2 antibody fragment to target the receptor on cancer cells and the C1C2 domain of lactadherin, which interacts with the EV membrane. By mixing mRNA-loaded EVs with purified chimeric protein, the EVs were endowed with targeting capability for HER2-overexpressing cancer cells. Delivery of these EVs followed by systemic administration of the prodrug 6-chloro-9-nitro-5-oxo-5H-benzo-(a)-phenoxazine (CNOB) resulted in near complete growth arrest of orthotopically implanted HER2-overexpressing breast tumors in mice.

This report establishes a new and versatile approach for improving GDEPT that could be applied to a wide variety of cancers and other diseases. Significant barriers to translation of this approach remain, most notably the problem of scalability of EV-based approaches. However, the methods and strategy described are likely to have broad utility in further developing both GDEPT and therapeutic EVs.