Researchers use single-cell imaging and mathematical modeling to determine effective drug properties

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Drug therapies that target a specific molecule have changed the way patients are treated for cancer and greatly improved survival rates. However, some patients do not respond to these therapies because the drug is not reaching the tumor cells effectively. In a new study published in *Scientific Reports*, Moffitt Cancer Center researchers combined single-cell imaging of cancer cells in mice with mathematical modeling to determine which drug characteristics are the most important for efficient drug uptake.

One of the inherent problems with targeted therapies is that tumors and their surrounding environment are complex and heterogeneous. Not all cells in a given tumor are alike. They can differ from one another in the expression of the targeted membrane receptors which may result in inadequate uptake and non-uniform response to the targeting drug. Additionally, the surrounding tumor environment is composed of different cell types with different properties and densities that can impact the ability of a drug to be effective.

These variations make it difficult to develop drugs that can effectively target all of the cells in a tumor. Furthermore, these cellular and genetic differences may cause a patient to be unresponsive to a cancer-targeted drug because some tumor cells may not be fully exposed to the drug and this incomplete exposure may enable these cells to develop drug resistance.

"Clinical success or failure of targeted therapy depends heavily on whether the drug molecules are able to reach all tumor cells and engage with their molecular targets to invoke the desired therapeutic effect," said Kasia A. Rejniak, Ph.D., associate member of the Department of Integrated Mathematical Oncology at Moffitt. This work was accomplished through collaboration between Rejniak computational group and the laboratory group of Dave L. Morse, Ph.D., associate member of the Department of Cancer Physiology.

The standard methods that scientists use to study drug uptake are based on the idea that a tumor and its surroundings have uniform characteristics. However, this assumption is inaccurate and may lead to a one-size-fits-all approach to treatment. The Moffitt research team wanted to take a different approach to study drug uptake. They used mathematical modeling and imaging techniques that allowed them to track and predict the ability of a single cell to take up a drug. Within their model, they compared different drug characteristics and tumor properties to determine which conditions lead to more effective drug uptake by a cell.

They discovered that the amount of drug that binds to a cell is dependent on how quickly a drug diffused through the tissue rather than on the concentration of drug that enters the tissue. Drugs that diffused quickly tended to bind more effectively to cells that were further away from blood vessels. Alternatively, drugs that diffused slowly tended to bind to cells that were closer to blood vessels and were more effective when the cells were tightly packed. The researchers also showed that drugs that are released quickly are able to bind more effectively to cells with different levels of drug receptors.

These discoveries suggest that changing different properties of a drug or the way a drug is administered may lead to increased delivery to tumor cells. "For example, to treat the fast-growing cells located near the vasculature, slowly diffusing agents may be beneficial. In contrast, for the dormant cells in poorly vascularized regions, the highly mobile agents may be preferential, or in some cancers, local injection directly to the tumor site may be beneficial," explained Rejniak. Ultimately, the researchers hope that their approach could eventually be used to design more personalized treatment options for cancer patients.

More information: Aleksandra Karolak et al, Targeting Ligand Specificity Linked to Tumor Tissue Topological Heterogeneity via

Single-Cell Micro-Pharmacological Modeling, *Scientific Reports* (2018).
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