Cancer treatment: reversing chemotherapy resistance

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By using the technique of computer-assisted molecular modelling, scientists have identified new compounds capable of blocking the protein principally responsible for the resistance of cancer cells to chemotherapy medications.

Chemotherapy medications are very powerful cellular poisons which kill cancer cells by preventing them from reproducing. It is for this reason that the majority of cancers are greatly reduced or even eradicated by chemotherapy (this is what is meant when it is said that tumors responded to treatment). Unfortunately, this positive response is sometimes temporary because it often happens that a subpopulation of the cancer cells manages to adapt to these poisons and thus becomes resistant to the collection of available medications. This phenomenon of resistance to multiple medications (multidrug resistance or MDR) is responsible for the majority of cancer recurrences and thus represents a major obstacle for the treatment of cancer.

POISON PUMPS

The emergence of this resistance to multiple chemotherapy medications is due to the activity of a family of transport proteins which literally pump these medications out of the cancer cells. By preventing the accumulation of medications inside the cancer cells, these pumps diminish or abolish the drugs' anticancer activities and thus allow the tumors to continue to grow even in the presence of these toxic medications.

The best known member of this family of pumps is P-glycoprotein (P-gp), a protein which is overexpressed in several types of cancers and which is responsible for resistance against most of the current chemotherapy medications, including taxanes (paclitaxel), vinca alkaloids (vinblastine) and anthracyclines (daunorubicin). The discovery of compounds capable of blocking the transport activity of P-gp could thus renew the sensitivity of cancer cells to several chemotherapy medications and thereby improve the response to treatments.

BLOCKING THE MOTOR OF THE PUMP

To identify compounds capable of interfering with the activity of P-gp, a group of American scientists used a very powerful supercomputer to model the interactions of this protein with a bank comprising over 15 million chemical compound structures. The objective of the study was to identify the molecules capable of specifically interacting with the "motor" of the pump, i.e. the portion of P-gp which binds ATP (the energy source used by cells) and which is necessary for the expulsion of medications by the pump. These strict selection criteria considerably reduced the number of candidates: from 15 million compounds initially, only 180,000 possessed the potential to bind to the motor of the pump

and only 4 of these (4 out of 15 million!) were actually capable of specifically blocking the activity of the protein inside the cells.

A more powerful analysis has shown that these compounds were actually capable of reversing the resistance to multiple chemotherapy medications within cancer cells, in that they permit different chemotherapy medications to enter the cells and accumulate there to reach concentrations sufficiently high as to cause cell death[1]. These compounds could serve as a springboard for the discovery of a new class of medications capable of countering the resistance of several cancers to current chemotherapy treatments. There is more hope in our war against cancer!

(1) Nanayakkara AK et al. Targeted inhibitors of P-glycoprotein increase chemotherapeutic-induced mortality of multidrug resistant tumor cells. Sci. Rep. 2018;8(1):967.

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