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Cover Story

Achilles heels and Trojan horses against drug-resistant tumor cells

Multidrug-resistance (MDR), an acquired or constitutive cross-resistance towards different anticancer drugs, is the first obstacle to a successful pharmacotherapy of cancer. Being present in 30–70% of tumors at diagnosis, it is even more frequent in metastasis and relapse phases [1]. Since it has been discovered that a crucial actor of MDR phenotype is P-glycoprotein (PGP), that actively extrudes a number of anti-cancer drugs outside tumor cells, several inhibitors of the pump have been designed. In parallel with the increasing number of pharmacological inhibitors, an increasing number of therapeutic failures have been accumulated, because of the low specificity, the high toxicity, the poor pharmacokinetic profile, the unfavourable drug–drug interactions [2]. On the other hand, extensive studies investigating how PGP works or which metabolic features of resistant cells sustain PGP enzyme have been performed, in order to identify eventual Achilles heels of MDR tumors [3].

In an article described in this issue, Professor Riganti and his coworkers found that cholesterol is the Achilles heel of MDR tumors [4]. Resistant cells have a tremendous need for cholesterol, that is highly incorporated in their plasma membrane and is crucial for the activity of PGP. Such a need appears so vital for MDR maintenance, that resistant tumors not only have high endogenous synthesis of cholesterol, but also they keep high levels of low density lipoproteins receptor (LDLR) to grant a further uptake of cholesterol from external environment. This is in opposition to each rule concerning the cholesterol homeostasis. In their work, Professor Riganti and his team has shown that MDR can be reversed by targeting the endogenous synthesis and the exogenous uptake of cholesterol. This result is obtained combining the anti-cholesterolemic drug simvastatin, one of the most widely-prescribed agents for cardiovascular diseases, and liposome-encapsulated doxorubicin, that has been clinically used for the treatment of breast and ovary metastatic cancers resistant to conventional chemotherapy.

By limiting the endogenous cholesterol synthesis with simvastatin, resistant cells show a lower cholesterol amount in plasma membrane and a lower activity of PGP. The tumor cells “physiologically” try to circumvent the lack of cholesterol exposing an increasing amount of LDLR. By masking the liposome-entrapped doxorubicin as LDL, Professor Riganti and his colleagues have obtained a secure way to make the anticancer drug enter into MDR cells. A synthetic peptide, containing the LDLR-binding site from human apoB100, is conjugated to the surface of the liposomal shell. Following this “Trojan horse” approach, the artificial particle loaded with doxorubicin (“apo-Lipodox”) is recognized by tumor cells as a true LDL and actively endocytosed via a receptor-driven

mechanism. Since doxorubicin is more uptaken by LDLR and less extruded by PGP, the drug accumulates within resistant cells and exerts significant cytotoxic effects. Interestingly the over-expression of LDLR is parallel with the presence of PGP in most tumors. Thus, the abundance of the former could be considered a new indirect marker of chemoresistance and a predictive factor of apo-Lipodox benefit. Drug-resistant cells, that have plenty of both LDLR and PGP, maximally take advantage from the combination of simvastatin and apo-Lipodox. On the other hand drug-sensitive cells, which poorly express LDLR and PGP, do not undergo over-toxicity. This looks particularly appealing if we consider that cardiomyocytes, the main target cells of doxorubicin's side-effects, have very low levels of PGP and LDLR.

From a general point of view the new tool proposed in this work (the association of statins and LDL-masked drugs) may represent a general approach to improve the delivery of several PGP substrates in districts rich of this transporter, such as the brain-blood barrier and the placental barrier. Moreover, a routine evaluation of the expression levels of PGP and LDLR on tumor specimens before starting a standard chemotherapy, may aid to select patients who will maximally benefit from this approach, leading to a more personalized chemotherapy. The drug delivery field has been focusing on drug targeting to tumor by a variety of means, and the new approach described by Professor Riganti and his team provides a new, highly effective approach.

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