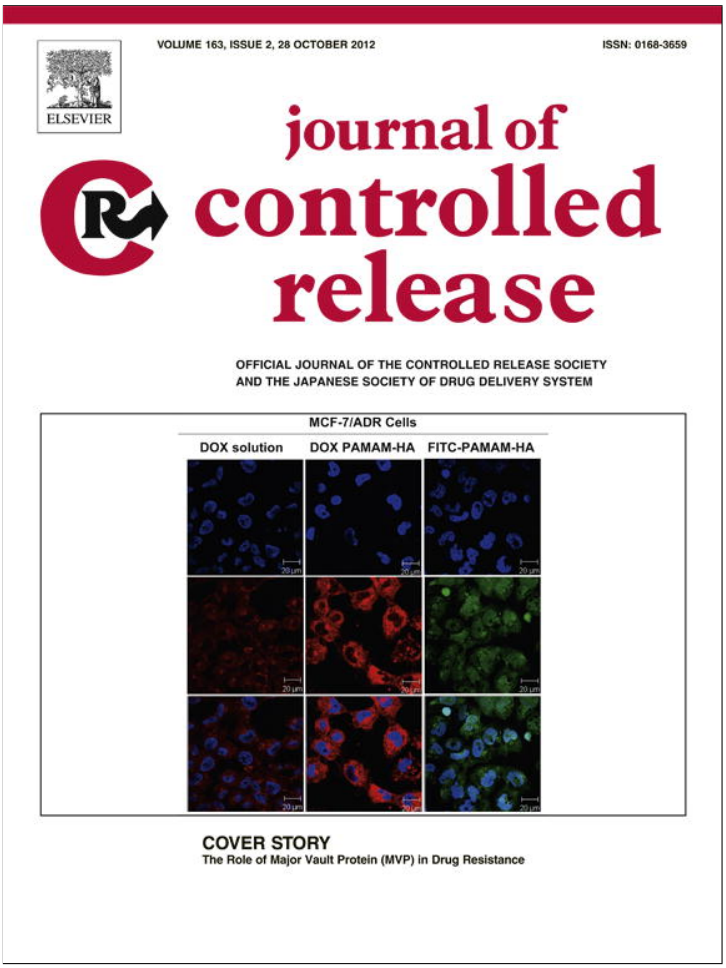

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Cover story

The role of major vault protein (MVP) in drug resistance

One of the major clinical obstacles in cancer therapy is the development of resistance by cancer cells to a multitude of chemotherapeutic agents, known as "multidrug resistance" (MDR). MDR occurs due to many factors, including increased efflux, blocked apoptosis, decreased drug influx, and altered cell cycle regulation. Of these mechanisms, overexpression of P-glycoprotein (Pgp) that is involved in drug efflux has received considerable attention, and naturally significant efforts have been devoted to inhibiting the function of Pgp with a hope of increasing intracellular accumulation of drug. Until now, however, few studies have investigated the intracellular drug distribution, e.g., in nucleus or in mitochondria, in MDR research.

Vaults are the largest cellular ribonuclear protein complexes with a hollow barrel-like structure, and have been associated with the MDR phenotype. The complex consists of three protein components, i.e., major vault protein (MVP), vault poly(ADP-ribose) polymerase (v-PARP), and telomerase-associated protein-1 (TEP1). MVP is the main component of vaults and is presumed to be involved in MDR. MVP is identical with the human lung resistance protein (LRP), known to be overexpressed in multiple chemotherapy resistance models. Many literatures have reported the relationship between vaults/MVP/LRP expression and drug resistance in clinical oncology. This is to clarify the expression status of MVP in human malignancies as a predictive and prognostic marker for the chemotherapy response and patient prognosis. Reports have indicated significant association between MVP expression and therapy response, patient prognosis (or survival rate) of many types of tumors, such as breast cancer, tongue carcinoma, myeloid leukemia, glioblastoma, and non-small-cell lung cancer.

MVP, having a molecular weight of 110 kD, is abundantly present in the cytoplasm of eukaryotic cells, and is upregulated in Pgp-negative chemoresistant cancer cell lines. This upregulation sometimes leads to a suggestion that MVP/vaults are involved in cellular detoxification processes, and consequently contribute to MDR by drug sequestration or shuttling drugs from the nucleus to cytoplasmic vesicles. There is some experimental evidence that vaults play a part in the extrusion of anthracylines from the nucleus [2]. Meanwhile, further studies are needed to clarify the detailed mechanisms and roles of MVP in cancer therapy because molecular mechanisms of how MVP is involved in drug resistance are still not been fully answered. Data on the clinical situation are less clear and it is still a matter of debate in how far MVP is involved in clinical therapeutic failure [3]. It is proposed that vaults may have a different intracellular distribution and/or function depending on the cell type.

In this issue, Professor Jian-Qing Gao and his colleagues proposed a nanocarrier made of polyamidoamine–hyaluronic acid (PAMAM–HA) that can co-deliver MVP-siRNA and doxorubicin (DOX) to MCF-7/ADR cells [4]. The nanocarrier escaped from the recognition of Pgp, thus resulting in enhanced DOX accumulation in MCF-7/ADR cells, and subsequentially released siRNA in cytoplasm to downregulate MVP expression. This allowed DOX to access to nucleus, ultimately reversing the drug resistance of MCF-7/ADR cells. Efficient intracellular delivery of siRNA led to satisfactory gene silencing effect as well as enhanced stability. Since drug resistance is one of the critical reasons leading to failures in many cancer chemotherapies, the MVP knockdown appears to be a valuable approach to increase the access of drugs to nucleus for much more efficient cytotoxicity. The work by Professor Gao and his team on efficient PAMAM–HA nanocarriers can be applied to delivery of other drugs and siRNA to downregulate expression of other proteins. Further studies are necessary to translate this finding to clinical applications, including the selected delivery of the nanocarrier to the target tumors. But considering all other factors are the same for different delivery systems, Professor Gao's nanocarrier presents an advantage over others in that it can escape from the recognition of Pgp for more efficient drug delivery to nucleus. This study is clearly a step in the right direction finding alternative avenues in overcoming MDR.

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