第 56 回　生体制御学セミナー

主催：埼玉大学生体制御学科

Development of potent non-toxic small molecule modulators/ inhibitors of ATP-binding cassette (ABC) drug transporters

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日 時:　２０１４年　９月２９日（月曜日）

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Development of potent non-toxic small molecule modulators/ inhibitors of ATP-binding cassette (ABC) drug transporters

Assoc. Prof. Dr. Pornngarm Dejkriengkraikul

Abstract

Our research is focused on the elucidation of the role of ATP-binding cassette (ABC) drug transporters in the development of multidrug resistance (MDR) in cancers and on the development of new therapeutic approaches to increase the efficiency of chemotherapy for cancer patients. For these studies

we are working with human P-glycoprotein (Pgp, ABCB1), multidrug resistance related protein 1 (MRP1, ABCC1) and mitoxantrone resistance protein (MXR, ABCG2).

To identify small molecule compounds that can reverse MDR, we have searched for effective plant-derived anticancer agents or their synthetic analogues. Incubating MDR cells with various concentrations of chemotherapeutic drugs in combination of a sublethal concentration of small molecule modulators/inhibitors, we identified the potent MDR chemosensitizers or modulators or inhibitors such as curcumin from *Curcuma longa*, stemofoline from *Stemona* spp., and kuguacin J from *Momordica charantia*. The mechanism of their effects was further analyzed by assessing the retention of calcein, rhodamine and anticancer drugs such as etoposide, doxorubicin, vinblastine and paclitaxel in both sensitive and resistant cell lines. Curcumin, α-asarone and β-asarone have been reported as effective chemosensitizers which could down-regulated both MDR1 gene expression and P-gp function in various types of human MDR cancer cells. While other natural products, such as stemofoline, kuguacin J, tetrandrine, schisandrin B and HZ08 inhibited only P-gp function, not gene expression. The molecular mechanisms of how the chemosensitizer could inhibit P-gp function either directly or indirectly will be discussed in more details. Furthermore, potentiation of the cytotoxicity of conventional chemotherapeutics to increase the eradication of cancer stem cells is one key strategy to cure cancer. These stem-like cancer cells are resistant to chemotherapy partly due to overexpression of ABC transporters. These non-toxic small molecule modulators/ inhibitors of ABC transporters might help to cure cancer stem cells.