S33-1 Studies on molecular mechanism of toxicity of anticancer drugs

◯Tsutomu TAKAHASHI[1], Akira NAGANUMA[1]

[1]Tohoku Univ., Grad. Sch. of Pharm. Sci.

The clinical utility of anticancer drugs is seriously limited by development of adverse effects and acquisition of resistance to these drugs by tumor cells. The mechanism underlying toxicity of anticancer drugs is still not fully understood. To elucidate more detailed mechanisms of toxicity of anticancer drugs, we performed a screen for determinants of sensitivity to adriamycin, an anthracycline antitumor antibiotic, using budding yeast as a model eukaryote. We found that overexpression of Akl1, a protein kinase of uncertain function, confer resistance to adriamycin. We investigated a function of Akl1 on adriamyicn resistance and found that downregulation of internalization step in endocytosis by Akl1 might be closely involved in the mechanism of adriamycin. In human cells, overexpression of AAK1, a human homologue of Akl1, also decreased adriamyicn toxicity, suggesting that downregulation of endocytosis via phosphorylaiotn might be involved in the acquisition of adriamycin resistance not only in yeast cells but also in human cells. Our result observation indicated a possibility that inhibition of internalization step in endocytosis facilitates transport of ubiquitinated protein from endoplasmic reticulum to vacuole, and decreases adriamycin toxicity. Detail further investigation on the relationship between endocytosis pathway and adriamycin toxicity might be helpful for improvements in the chemotherapy with adriamycin.