CDB SEMINAR


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Friday, March 23, 2007

16:00~17:00 C1F CDB Auditorium

## MOLECULAR MECHANISM OF ANT-CANCER THERAPIES


**Summary**

Cell cycle checkpoints prevent transition from one phase of the cell cycle to the next until all processes of the present phase are completed. Defects in these checkpoints result in gene mutations and chromosome damage, which lead to the development and progression of malignant tumors. However, loss of checkpoint function is thought to be responsible for their sensitivity to antineoplastic treatments such as chemotherapy and radiation. Most cancer cells are deficient in G1 checkpoint function and therefore fail to arrest in G1 phase on exposure to genotoxic agents. Instead, they accumulate temporarily in G2 phase. However, given that the G2 checkpoint is also partially impaired in cancer cells, they are unable to maintain G2 arrest and eventually die as they enter mitosis. This process is known as mitotic catastrophe or mitotic death.

Mitotic catastrophe is an important mechanism for the induction of cell death in cancer cells by antineoplastic agents. We characterized the dynamics and regulation of mitotic catastrophe induced by anti-microtubules agents such as paclitaxel by using time-lapse microscopy. Cells entering mitosis arrested at metaphase without chromosome segregation and subsequently collapsed. In the metaphase-arrested cells, mitotic checkpoint was activated. Furthermore, inhibition of mitotic checkpoint function as a result of depletion of BubR1 or Mad2 by RNAi led cells to escape from mitotic catastrophe and to undergo mitotic slippage. Our data suggest that dysfunction of the mitotic checkpoint in cancer may confer resistance to anti-microtubules agents.

To identify the critical signal pathways to regulate the paclitaxel-induced mitotic catastrophe, activation of various kinases were examined. Among diverse intracellular kinases, p38 MAP kinase was significantly and specifically activated when cells underwent mitotic death. The activation of p38 requires the long-term metaphase arrest and is triggered as cell goes from metaphase to anaphase. Moreover, we found that the p38 activation is induced by the oxidative stress which is increased during metaphase arrest. Therefore, treatment with either anti-oxidants or p38 inhibitor suppressed the paclitaxel-induced mitotic catastrophe. Based on these data, we would like to propose the new resistance mechanisms against chemotherapeutic agents in the symposium.



**Host:**

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