CDB SEMINAR

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16:00~17:00 A7F Seminar Room

Cell-based screen for altered nuclear phenotypes to reveal the nuclear events regulating cellular senescence

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Summary

Cellular senescence is a state of irreversible cell cycle arrest induced by various cytotoxic stressors mostly accompanied by DNA damage induction. Increasing evidence shows that cellular senescence cause decline in the function of tissues, which is associated with aging of individuals. It is also believed that cellular senescence contributes to tumor suppression by inducing stable cell cycle arrest. Therefore, the search for factors that induce cellular senescence can contribute to understanding molecular mechanisms of senescence/aging or to development of therapeutic strategies for cancer. We established a simple cell-based screen for senescence-inducing agents by looking for any changes in nuclear appearance associated with cellular senescence. In the screening, we focused on two phenotypic changes; an enlargement in nuclear size and a formation of nuclear foci, which are often associated with senescence and can be easily visualized by DNA staining. Multiple hit compounds were found to be an inhibitor of Aurora kinase B (AURKB), and they indeed induced cellular senescence accompanied by accumulation of tetraploidy in cells. The stressor which triggers senescence remains elusive, but we found that this type of senescence was not associated with accumulation of γ-H2AX, suggesting the lack of DNA damage before senescence induction. We also found some hit compounds that induced appearance of nuclear foci, which displayed features of senescence-associated heterochromatic foci (SAHF). SAHFs are formed through a spatial repositioning of heterochromatin, and we have found that the SAHF formation is promoted by a decrease in nuclear level of lamin B1 (LMNB1). Our present attempts include an identification of target molecules, which may regulate spatial redistribution of chromatin during cellular senescence.

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