CDB SEMINAR

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16:00~17:00 A7F CDB Conference Room

A paradoxical role of HMGA proteins in tumor suppression and tumorigenesis

Summary

Cellular senescence is a stable state of proliferative arrest that provides a barrier to malignant transformation and contributes to the anti-tumor activity of certain chemotherapies. Senescent cells can accumulate senescence-associated heterochromatic foci (SAHFs), which may provide a chromatin buffer that prevents activation of proliferation-associated genes by mitogenic transcription factors.

To further understand the significance of chromatin structural changes in senescence, we take a biochemical approach to characterize the chromatin composition of senescent cells. Our data show that the High Mobility Group A (HMGA) proteins accumulate on the chromatin of senescent fibroblasts and are essential structural components of SAHFs. This is surprising because HMGA proteins are typically associated with gene activation and have been linked to cellular proliferation. Indeed, HMGA has been classified as an oncogene. We show that HMGA proteins cooperate with the $p16^{INK4a}$ tumor suppressor to promote SAHF formation and proliferative arrest, and stabilize senescence by contributing to the repression of proliferation-associated genes. These anti-proliferative activities are canceled by co-expression of the *HDM2* and *CDK4* oncogenes, which are often co-amplified with *HMGA2* in human cancers.

We also conducted a series of microarray experiments to identify genes affected by HMGA proteins in normal and senescent cells. Interestingly, the data indicate a prominent role for HMGA in gene repression during senescence. Furthermore, most of the genes controlled by HMGA proteins in senescent cells were distinct from those affected by HMGA proteins in normal cells, indicating that HMGA proteins regulate gene expression depending on cellular contexts. Altogether, our results identify a new component of the senescence machinery that contributes to heterochromatin formation, and imply that HMGA proteins can act in tumor suppressor and oncogene networks depending on the contexts.

References

Narita M. *et al*., **Cell** 126: 503-14 (2006)

Narita M. *et al*., **Cell** 113:703-16 (2003)

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