News Release

Title

Pericentromeric noncoding RNA changes DNA binding of CTCF and inflammatory gene expression in senescence and cancer

Key Points

- **Noncoding RNA derived from pericentromeric repetitive sequences provokes inflammatory gene expression in senescence and cancer.**

Summary

Cellular senescence causes a dramatic alteration of chromatin organization and changes the gene expression profile of proinflammatory factors, thereby contributing to various age-related pathologies through the senescence-associated secretory phenotype (SASP). Chromatin organization and global gene expression are maintained by the CCCTC-binding factor (CTCF); however, the molecular mechanism underlying CTCF regulation and its association with SASP gene expression remains unclear. We discovered that noncoding RNA (ncRNA) derived from normally silenced pericentromeric repetitive sequences directly impairs the DNA binding of CTCF. This CTCF disturbance increases the accessibility of chromatin and activates the transcription of SASP-like inflammatory genes, promoting malignant transformation. Notably, pericentromeric ncRNA was transferred into surrounding cells via small extracellular vesicles acting as a tumorigenic SASP factor. Because CTCF blocks the expression of pericentromeric ncRNA in young cells, the down-regulation of CTCF during cellular senescence triggers the up-regulation of this ncRNA and SASP-related inflammatory gene expression. In this study, we show that pericentromeric ncRNA provokes chromosomal alteration by inhibiting CTCF, leading to a SASP-like inflammatory response in a cell-autonomous and non–cell-autonomous manner and thus may contribute to the risk of tumorigenesis during aging.

Research Background

Senescence is a state of essentially irreversible cell cycle arrest induced by several stressors, i.e., aging, obesity, radiation, and chemotherapy. Senescent cells that accumulate *in vivo* during aging communicate with surrounding tissues through the production of proinflammatory proteins, termed the senescence-associated secretory phenotype (SASP), which plays multiple physiological and pathological roles. In aged individuals, inflammatory SASP factors promote numerous age-related diseases, including cancer. Therefore, elucidating the regulatory mechanism of the SASP is essential for developing new preventive and therapeutic strategies against age-related cancer.

Research Results

A team of JFCR, Nagoya University, *etc.* researchers has hypothesized that an aberrant

chromatin architecture observed in senescent cells might be associated with the SASP and have commenced the analysis of genome-wide chromatin interaction and gene expression using next-generation sequencing techniques. They revealed that the region containing pericentromeric repetitive sequences called human satellite II (hSATII), which are epigenetically silenced in normal cells, showed a notably open state in senescent cells. In addition, the expression of noncoding RNA (hSATII RNA) was markedly upregulated during cellular senescence. Further analysis revealed that hSATII RNA upregulated SASP-like inflammatory gene expression by disturbing chromatin interactions in some SASP gene regions through the functional impairment of CCCTC-binding factor (CTCF), which is important for the maintenance of genomic integrity.

"Small extracellular vesicles (EVs) secreted from cancer and stromal cells dynamically contribute to tumor incidence and progression in a non–cell-autonomous manner in the tumor microenvironment. Intriguingly, the amounts of hSATII RNA were higher in small EVs derived from senescent cells than in those derived from proliferating cells. Thus, our data suggest that hSATII RNA derived from senescent stromal cells are transferred into surrounding cells through small EVs and function as a SASP-like inflammatory factor in the tumor microenvironment."

Further, the researchers found that hSATII RNA was highly detectable in cancer cells in surgical specimens from patients with primary colon carcinoma. Strikingly, the population of hSATII RNA-positive cells was significantly higher among cancer-associated fibroblasts than fibroblasts in normal stromal tissues.

Research Summary and Future Perspective

Noncoding RNA derived from pericentromeric repetitive sequences provokes inflammatory gene expression in senescence and cancer. These findings highlight the new role of the hSATII RNA, which supports tumor development in a non–cell-autonomous manner via the secretion of SASP-like inflammatory factors and small EVs. Understanding this molecular mechanism can facilitate the development of novel preventive and therapeutic strategies against age-related pathologies in the future.

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