第 457 回つくば分子生命科学セミナー

TSUKUBA MOLECULAR LIFE SCIENCE SEMINAR

演題：Clone wars: the emerging role of telomerase in stem cell competition

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会場：イノベーション棟 105 室

要旨：

Tissue development and homeostasis are shaped by cell competition, a mechanism for culling unfit cells based on differences in expression of key regulatory genes. During carcinogenesis, oncogenic mutations confer a competitive growth advantage through an analogous process. Here, we show that the telomerase reverse transcriptase (TERT) is required for the competitive clone formation in spermatogonial stem cells (SSCs) independent of its telomerase activity.

TERT is the catalytic subunit of telomerase, the ribonucleoprotein complex that elongates telomere repeats at the end of each chromosome. Germline mutations that inactivate telomerase promotes telomere shortening and subsequent premature aging. Conversely, telomerase upregulation is characteristic of more than 90% of human cancers and confers extensive proliferation potential. These genetic findings from humans indicate that modest changes in TERT levels influence cell fate and the likelihood of malignant transformation. However, it remains unclear whether expression changes in TERT affect clonal behavior during homeostasis and carcinogenesis. Using lineage-tracing, we find that TERT-expressing SSCs yield long-lived clones, but that selective TERT-deletion in these SSCs disrupts competitive clone formation by promoting differentiation. This requirement for TERT is independent of catalytic activity and the canonical telomerase complex. Loss of TERT induces a genome-wide reduction in open chromatin and causes reduced activity of the MYC oncogene, an established mediator of cell competition. Transgenic expression of MYC in TERT-deleted SSCs restores MYC-target gene expression and rescues clone formation. These data reveal an unexpected role for TERT in promoting enhanced stem cell competition and genetic link between two oncogenes TERT and MYC.

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