Taken together, our results revealed the novel mechanism by which HNF-4α increased ChREBP transcription in response to glucose in liver cancer cells.

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### CANCER-ASSOCIATED FIBROBLASTS PROMOTES TUMOR RELAPSE AFTER RADIOTHERAPY

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Tumor relapse after radiotherapy is a big challenge to oncologists. Here, we discovered that cancer-associated fibroblasts (CAFs), a major component of cancer stromal cells, promote cancer cell recovery and tumor relapse post-radiation. We provided evidences that CAFs-produced cytokines/chemokines and intermediate metabolites are capable of inducing autophagy in cancer cells post-radiation and promoting cancer cells recovery from radiation-induced damage in vitro and in mice, which was consistent with our clinical observation that the newly developed image-guided stereotactic body radiation therapy (SBRT) was less effective than the conventional external beam radiotherapy (EBRT) in term of recurrence and survival of cancer patients. Mechanistically, CAF-derived cytokines maintained the redox homeostasis post-radiation and increased ROS level compared to control irradiated cancer cells, ROS enhanced the activity of PP2Ac through a reversible sulfenylation on the cysteine residue in the motif of HC(X)4EXV, similar as the motif of HC(X)5RS/T in PTPs (protein tyrosine phosphatases), distinct from the sulfenylation of HC(X)5RS/T motif, which inactivates the activity of PTPs. Moreover, the inhibition of autophagy abolished the CAF-promoted tumor relapse post-radiotherapy. Taken together, our findings demonstrate that CAFs promote cancer cell recovery and tumor regrowth post-radiation, suggesting CAFs are critical for tumor recurrence after radiation and autophagy pathway is a therapeutic target for radiotherapy sensitization.

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### THE ROLE OF AUTOPHAGIC DEGRADATION IN CANCER TREATMENT

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Autophagy is an evolutionarily conserved protein degradation pathway in eukaryotes that plays key role in a number of pathological conditions including cancer. Understanding the mechanism of autophagy will offer hope for the development of new therapeutic approaches for cancer treatment. To elucidate the role of autophagy in tumorigenesis or tumor progression, we explored the expression of autophagy-associated proteins in tumor tissues. Our results showed that low expression of Beclin 1 was significantly associated with poor prognosis in ovarian tumors, colon cancers with stage IIIB, lymphoma. We also found that the patients with lower level of ULK1 had a significant shorter cancer-related survival time and distant metastasis-free survival time. To understand whether anticancer drugs induces autophagy in cancer cells, topotecan and ceramide were employed. The results showed that activation of JNK pathway can phosphorylate c-Jun and promote c-Jun binding to the promoters of Beclin 1, LC3 and Sestrin 2 to upregulate Beclin 1, LC3 and Sestrin 2 expression, which plays a key role in anticancer agents-induced autophagy in cancer cells. We also found that Beclinacetylated by p300 at lysine residues 430 and 437. The phosphorylation of Beclin 1 at S409 by CK1 is required for the subsequent p300 binding and Beclin. Beclin 1 acetylation inhibits autophagosome maturation and endocytic trafficking by promoting the recruitment of Rubicon. In tumor xenografts, the expression of 2KR mutant Beclin 1 leads to enhanced autophagosome maturation and tumor growth suppression. In order to explore the role of autophagy in cancer treatment, our investigation showed that Rhabdastrellic acid-A, an isomalabaricane triterpenoid isolated from the sponge Rhabdastrella globostellata, induced autophagy of cancer cells. SYUIQ-5, previously identified by us as a novel G-quadruplex stabilizer and potent telomerase inhibitor, inhibited proliferation of cancer cells, triggered a rapid and potent telomere DNA damage response and obviously induced autophagy. These phenomena may primarily depend on the delocalization of TRF2 from telomere. We found that wild-type p53 can activate AMPK, inhibit mTORC1 and promote colon cancer cells survival by enabling cytoprotective autophagy in response to topotecan treatment. In contrast, the inhibition of autophagy alleviated the anti-tumour effect of topotecan treatment in p53 mutant or knockout colon cancer cells both in vitro and in vivo. We also found that topotecan, a topoisomerase I inhibitor, and cisplatin induced DNA damage and activated ATM, which phosphorylates PTEN at serine 113 and further regulates PTEN nuclear translocation in A549 and HeLa cells. After nuclear translocation, PTEN induces autophagy, in association with the activation of the p-JUN-SESN2/AMPK pathway, in response to topotecan. Our researches show that decreased autophagy-related protein expression is associated with tumor progression and poor prognosis in ovarian cancer, breast cancer, colon cancer. We also found that some anticancer agents-mediated autophagy-associated cell death or survival dependent of cancer cell context. Therefore, understanding the mechanisms of autophagy and the role of autophagy in cancers will facilitate novel therapeutics for cancer.

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### SIRT1 IN TUMOR METABOLISM AND TUMORIGENESIS

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SIRT1, the most conserved NAD+-dependent protein deacetylase, is an important cellular metabolic and stress sensor. However, the role of this critical factor in cancer development remains unclear and inconclusive. SIRT1 has been shown to directly maintain genome stability and repress inflammation, thereby decreasing tumor growth. On the other hand, SIRT1 also has been reported to inhibit activities of tumor suppressors, promoting growth and survival of cancer cells. As a result, whether SIRT1 is an oncogene or tumor suppressor remains controversial.
We recently explored the possibility that SIRT1 regulates cancer development in a quantitative dose-dependent manner. We hypothesized that different SIRT1-regulated cellular pathways have distinct sensitivities to changes of SIRT1 dosages. These distinct sensitivities may differentiate the outcomes in cancer cell proliferation and growth, contributing to observed dual functions of SIRT1 in tumor development.
To test this hypothesis, we generated immortalized mouse embryonic fibroblasts (MEFs) and human colorectal cancer cell lines carrying two copies (WT), one copy (Het), or no copy (KO) of SIRT1 gene. Consistent with our hypothesis, SIRT1 Het cells displayed elevated proliferation in culture, increased colony formation on soft agar, and enhanced tumor formation in nude mice in a xenograft model, whereas SIRT1 KO cells exhibited reduced proliferation, colony formation, and cancer formation. Further mechanistic studies revealed that deletion of one copy of SIRT1 gene is sufficient to activate NF-κB and induce c-Myc expression, promoting cell proliferation, autophagy, and stress resistance in a glutamine-dependent manner. Deletion of both copies of SIRT1 gene, on the other hand, triggers cellular apoptotic pathways, leading to increased cell death, diminished autophagy, and reduced cancer formation. Consistently, intestine-specific SIRT1 heterozygous mice have enhanced intestinal tumor formation, whereas intestine-specific SIRT1 homozygous knockout mice have reduced development of colon cancer. Finally, expression levels of SIRT1 are reduced in human colorectal tumors, and reduced tumor SIRT1 expression correlates with poor prognosis in colorectal cancer patients.
In summary, our findings indicate that the dose-dependent regulation of tumor metabolism and possibly apoptosis by SIRT1 mechanistically contributes to the observed dual roles of SIRT1 in tumorigenesis. Our study highlights the importance of maintenance of a suitable SIRT1 dosage for metabolic and tissue homeostasis, which will have important implications in SIRT1 small molecule activators/inhibitors based therapeutic strategies for cancers.

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