Sirt1 is a tumor promoter in lung adenocarcinoma

Chen, Xue

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Sirt1 is a tumor promoter in lung adenocarcinoma

肺腺癌における Sirt1 の役割についての研究

神戸大学大学院医学研究科医科学専攻

病理病態学

（　指導教員：林祥剛教授　）

陳　　雪

Cellular senescence and apoptosis are potent tumor suppression mechanisms for the regulation of cell growth arrest and limitation of aberrant cell proliferation. It has been noted that Sirtuin1 can repress cellular apoptosis and senescence to affect DNA repair, stress response, and aging. Aging is often related to the incidence of cancer, including human primary lung adenocarcinoma. Silent information regulator 2 (Sir2) has been reported that extends the lifespan up to 70% in budding yeast. Mammals possess seven homologs of yeast Sir2, which are known as the Sirtuin family (Sirtuin1-7). Sirtuin1 (Sirt1) is one member of Sirtuin family that is the most thoroughly studied. And Sirt1 is similar to yeast Sir2, which is a nicotinamide adenine dinucleotide (NAD+)–dependent class III histone deacetylase. The foremost function of Sirt1 is to deacetylate histone proteins such as H1, H3, H4, and non-histone proteins such as p53, FOXO and so on. It, with its wide distribution in cell nucleus and cytoplasm，has been found to regulate a series of normal physiological processes, and there are vast numbers of down- and up-stream molecules of Sirt1. Interestingly, a few down-stream molecules of Sirt1, such as E1F2, p53, are also considered to be up-stream molecules. Moreover, previous studies have reported that Sirt1 is considered to play the part of both a tumor promoter and tumor suppressor in tumorigenesis. These seemingly contradictory roles show that Sirt1 has a complicated function in tumorigenesis. In one word, the function of Sirt1 depends on the temporal and special distribution of different its upstream regulators and downstream targets in different tissue contexts. Some of previous data have provided strong evidence that Sirt1 is significantly overexpressed to function as a tumor promoter in mouse and human prostate cancer and acute myeloid leukemia. However, some studies indicated

that Sirt1 is an inhibitor in tumorigenesis such as colon cancer. Until now, it is still unknown how Sirt1 is expressed in primary lung carcinoma patients.

For this purpose, we analyzed data for 125 patients (71 males, 54 females) who underwent surgical operation for primary lung adenocarcinoma after being diagnosed and treated at Kobe University Hospital, Japan between 2001 and 2004. The all of specimen of patients of lung adenocarcinoma by immunohistochemistry staining. For the assessment of the protein expression of Sirt1, samples were classified as Sirt1-positive if the ratio of stained cells in all epithelial cancer cells of a tumor tissue was 60% or more, and as Sirt1-negative if it was less than 60%. Sixty percent was used as the cut-off value because it was statistically useful for this study.

In our study, we found that overexpression of Sirt1 is close related to Ki67 index ($P=0.002$), and high TNM classification ($p=0.002$), especially in lymph nodes invasion (pN) ($p=0.018$) and metastasis (pM) ($p=0.048$). Moreover, overexpression of Sirt1 showed significant association with pulmonary vein invasion ($p=0.004$) and lymphatic duct invasion($p=0.039$) , but without pulmonary arteries ($p=0.261$). We also found a significant negative regulation between HIF1 (Hypoxia-inducible factors1) expression level and Sirt1-positive signal in primary lung adenocarcinoma patients.

HIF1 is a member of the HIF family that function as regulators and increase when cells become hypoxia due to oxidative stress. It has been reported that the high level of HIF1 expression is associated with a good prognosis for lung cancer. HIF1 levels frequently increases in the very early stages of tumor progression, is expressed in situ carcinomas and premalignant tissues. The function of HIF1 could to decrease cell hypoxia and induce cell apoptosis. On the contrary, one of the functions of Sirt1 is to enhance the chance of cell survival, with excellent growth and proliferation

under hypoxic conditions. As our result, we found the negative regulation between HIF1 expression and Sirt1- positive expression. Moreover, the situation of cells located in oxygen-poor condition, frequently occurs in medium-term and advanced stages of cancer. These adaptable cells adapt to hypoxia and survive through Sirt1 regulation probably have a more aggressive phenotype and reduce sensitivity to anti-cancer treatment. Form this result, we suggest that Sirt1 is participated in the initiation of tumors, furthermore its expression more closely relate to medium-term and advanced stages of cancer and tumor development. Sirt1 maybe thus be related to a poor prognosis for lung adenocarcinoma. In addition, hypoxia and oxidative stress can cause DNA damaged, Sirt1 also plays a positive role in repairing double-strand DNA breaks. Erroneous DNA replication or repair causes unceasing proliferation of aberrant cells as a function of Sirt1 and the probability is high for these cells to become tumor. With an increase in age, some inhibitors of Sirt1 function, such as HIC1, DBC1 become weaker. They repress Sirt1 expression in normal cells, but with aging of the cells, they may gradually lose their function to promote tumorigenesis.

Ki67 index and TNM classification is also important indicator for clinical tumor development. The high Ki67 index and TNM classification indicate that cancer cell have a faster growth and differentiation in tumorigenesis, further there is a strong possibility to invade the surrounding tissue and metastasize to other areas. These usually occur in malignant tumors and are both associated with a poor prognosis for lung adenocarcinoma patients. In our investigation, we found that high Ki67 index and TNM classification are close correlation with Sirt1- positive expression. Particularly, in TNM classification, Sirt1-positive expression more close related to lymph node invasion and metastasis, but not tumor size. Thus it can be seen that overexpression of Sirt1 tightly relate to invasion and metastasis. It is suggested that

overexpression of Sirt1 be related to a poor prognosis for lung adenocarcinoma once more. These suggest that finding an inhibitor based on the biologic features of Sirt1 might make Sir1 an ideal target for the development of potent anti-cancer drugs.

神戸大学大学院医学(系)研究科（博士課程）

論文審査の結果の要旨			
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（要旨は１，０００字～２，０００字程度）

Sirtuin1 is a nicotinamide adenine dinucleotide (NAD+)–dependent class III histone deacetylase. It reportedly can repress cellular apoptosis and senescence to affect DNA repair, stress response, and aging. Interestingly, previous data indicated that Sirt1 is thought to be both a tumor promoter and a tumor suppressor in tumorigenesis. However, Sirt1 expression in primary lung adenocarcinoma remains unknown.

Xue Chen and co-workers analyzed data for 125 patients (71 males, 54 females) who underwent surgical operation for primary lung adenocarcinoma after being diagnosed and treated at Kobe University Hospital between 2001 and 2004. The all of specimen of patients of lung adenocarcinoma by immunohistochemistry staining. For the assessment of the protein expression of Sirt1, samples were classified as Sirt1-positive if the ratio of stained cells in all epithelial cancer cells of a tumor tissue was 60% or more, and as Sirt1-negative if it was less than 60%. Sixty percent was used as the cut-off value because it was statistically useful for this study.

In this study, the authors found that overexpression of Sirt1 is close related to Ki67 index (P=0.002), and high TNM classification (p=0.002), especially in lymph nodes invasion (pN) (p=0.018) and metastasis (pM) (p=0.048). Moreover, overexpression of Sirt1 showed significant association with pulmonary vein invasion (p=0.004) and lymphatic duct invasion(p=0.039) , but without pulmonary arteries (p=0.261). They also found a significant negative regulation between HIF1 (Hypoxia-inducible factors1) expression level and Sirt1-positive signal in primary lung adenocarcinoma patients.

In conclusion, overexpression of Sirt1 is related to a poor prognosis for lung adenocarcinoma and finding an inhibitor based on the biologic features of Sirt1 might make Sir1 an ideal target for the development of potent anti-cancer drugs.

The candidate, Xue Chen, having complete studies on Sirt1 expression in primary lung adenocarcinoma, and having advanced the field of knowledge in the area of lung cancer, is hereby recognized as having qualified for the degree of Ph.D. (Medicine).