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Inhibition of sirtuin-1 activity as a potential therapeutic strategy for pediatric soft tissue sarcomas.

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Sirtuins are a NAD+ dependent class III histone deacetylases with a variety of histone and non histone substrates.
Seven sirtuins (sirT 1-7) have been identified in mammals. SirT1 has been implicated in the regulation of glucose and lipid metabolism during cellular stress conditions like fasting and calory restriction. In addition of its functions in cell metabolism, SirT 1 has been implicated in tumor progression since it mediates the deacetylation of several cancer associated transcription factors like p53, NFkB and FOXO proteins.
We have analyzed the expression of sirT1 and sirT2 in a serie of synovial sarcoma tumors and cell lines and evaluated the activity of the sirtuin inhibitor tenovin-6, in synovial sarcomas and rhabdomyosarcomas. We found that sirT1 was overexpressed in synovial sarcomas biopsies and cell lines in comparison to normal mesenchymal cells. Exposure of synovial sarcoma and rhabdomyosarcoma cell lines to tenovin-6, inhibited tumor cell proliferation and induced the expression of the cyclin dependent kinase inhibitor p21 independently of p53 expression and acetylation. Tenovin 6 anti-tumour activity was associated with decreased de-acetylating activity of nuclear and cytoplasmic sirtuins including sirT1.
Combination of tenovin 6 with doxorubicin had a synergistic anti-proliferative effect in synovial sarcomas. In addition, the combination of tenovin-6 with the multikinase inhibitor Sorafenib, had a significant anti-tumor growth effect on synovial sarcoma and rhabdomyosarcoma cell lines. Rhabdomyosarcoma xenografts treated with tenovin 6 had a decreased tumour mass as compared to placebo treated controls. The treated tumors up-regulated cytoplasmic sirT2 and displayed nuclear tranlocation of p53.
Our results indicate that overexpression sirT1 can be associated with the pathogenesis of synovial sarcoma and rhabdomyosarcoma and that the pharmacological inhibition of sirtuin activity is a potential therapeutic strategy for these tumors.

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