Synovial Sarcoma Chromatin Dynamics Reveal a Continuum in SS18::SSX Reprograming

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Scientific abstract:

Background and Rationale: Synovial sarcoma (SyS) is an aggressive soft tissue malignancy characterized by a pathognomonic chromosomal translocation leading to the formation of the SS18::SSX fusion oncoprotein. Previous research shows that SS18::SSX associates with BAF, a chromatin remodelling complex, suggesting deregulation of the chromatin architecture as the oncogenic driver in this tumour type. SyS show few recurrent genetic alterations beyond SS18::SSX but display varying clinical and histological presentation. We hypothesized that, given the lack of driving secondary alterations, the observed clinical heterogeneity might be explained by epigenetic heterogeneity.

Objective: Reveal epigenetic patterns within synovial sarcoma cells in hopes of uncovering novel therapeutic avenues for patients.

Methods: We performed multi-omics analysis on 52 primary human SyS tumors using RNA-seq, WGS, WGBS and ChIP-seq (up to eight histone marks). Survival data was acquired. NanoString and immunohistochemistry were done on pathology samples. Machine learning was leveraged to develop a bivalency signature for prognostication. Cell viability assays provided drug vulnerability data.

Results: Our analysis revealed a continuum of epigenomic states across the cohort at fusion target genes independent of recurrent genetic changes. We identify subtypes of SyS defined by enhancer states and reveal unexpected relationships between H2AK119Ub and active marks. The number of bivalent promoters, dually marked by the repressive H3K27me3 and activating H3K4me3 marks, has strong prognostic value and outperforms tumor grade in predicting patient outcome. Finally, we identify defining SyS epigenomic features including H3K4me3 expansion associated with striking DNA hypomethylation of promoter regions in which SyS display the lowest mean methylation level of any sarcoma subtype. We explore this feature as a potential vulnerability in SyS cell lines and identify WRD5 inhibition through OICR-9427 treatment as a promising therapeutic strategy.

Conclusions: Primary pre-treatment SyS epigenomes are highly heterogenous including a continuum in the number of bivalent promoters at SS18-SSX target genes. Distinctive, potentially unique, aspects of the SyS epigenome include aberrant repressive mark relationships, and DNA hypomethylation. These novel insights have uncovered potential prognostic and therapeutic opportunities for SyS.

Anticipated Impact: SyS tumours have distinct and heterogenous epigenomic landscapes that can inform prognosis and have revealed WDR5 inhibition as a potential therapeutic vulnerability.

Plain language abstract:

Background and Rationale: Synovial sarcoma is a type of cancer that occurs in connective tissues and often effects young adults. Doctors rely on surgery and radiation to treat synovial sarcoma, as chemotherapy has not shown to improve survival. Unfortunately, currently available treatments are not enough to cure patients when the cancer spreads from the primary location. Synovial sarcoma is defined by the joining of two segments of DNA, one segment holds the instructions for the protein SS18 and the other for the protein SSX, this results in a combined protein, called SS18::SSX. The fusion protein incorporates into important cellular protein complexes and changes how the cells can read their DNA, a level of cellular regulation that is called epigenetics. The epigenetic profiles of cells can be measured by looking at what regions of DNA are flagged with specific chemical modifications, called epigenetic marks.

Objectives: We hope to better understand how SS18::SSX is altering how synovial sarcoma cells can read and interact with their DNA to uncover new therapies for patients.

Methods: The epigenetic profiles of cells can be measured by looking at what regions of DNA are flagged with specific chemical modifications, called epigenetic marks. The flagged regions can then be sequenced, where the DNA code is read and recorded, telling us where these marks are found along the DNA. To investigate the changes that the fusion protein causes within cells, we looked at where the epigenetic marks are found in 52 synovial sarcoma tumours.

Results: We found that there is a range in where the epigenetic marks are found across the 52 tumours. Further, our investigation demonstrated that among synovial sarcoma tumours, there are unexpected relationships between different types of epigenetic marks that are not normally seen in healthy cells or other cancer types. These unique characteristics reveal insight into the cell type that synovial sarcoma develops from, presents a new way to predict patient survival, and reveals a potential weakness in the synovial sarcoma cancer cells that can be targeted by new treatments.

Conclusions/Anticipated Impact: Our study explores how the fusion protein, SS18::SSX, in synovial sarcoma tumours alters how cells can read their DNA, informing how we can predict patient outcomes and revealing a potential new treatment for synovial sarcoma patients.