TOP 10 RESEARCH ACHIEVEMENTS

Epigenetic Reprogramming of Cancer via Microenvironment Engineering

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In many cancers, tumour progression is associated with increased tissue stiffness. Yet the mechanisms associating tissue stiffness with tumorigenesis and malignant transformation are unclear. We show that the stiffness of the extracellular matrix of gastric cancer reversibly regulates the DNA methylation of the promoter region of the oncogenic Yes-associated protein (YAP). Our findings offer the insight into promising mechanotherapeutic strategies specifically targeting the mechanical properties of the ECM, to regulate epigenetic status and oncogenic transcription activity of malignant tumor cells.

1. Background

Extracellular cues are recognized as potent regulators of epigenetics in the development and progression of solid tumours. Among the extracellular signals, increased extracellular matrix (ECM) stiffness is closely associated with pathological states and is considered a critical factor that precedes tumorigenesis. While it remains unclear exactly how ECM stiffening causes the malignant phenotype of cancer cells, there is evidence that external biophysical cues can be mechanically transmitted via cytoskeletal tension into the nucleus, impacting gene expression through mechanosensors and intracellular mechanotransducers, such as Yes-associated protein (YAP). Although mechanical stimulus is recognized as a crucial determinant of cancer cell fate, hinting at the involvement of epigenetic regulation, it remains unclear whether YAP activation by matrix stiffness is accompanied by epigenetic changes, and whether any such effects are reversed by matrix stiffness alteration.

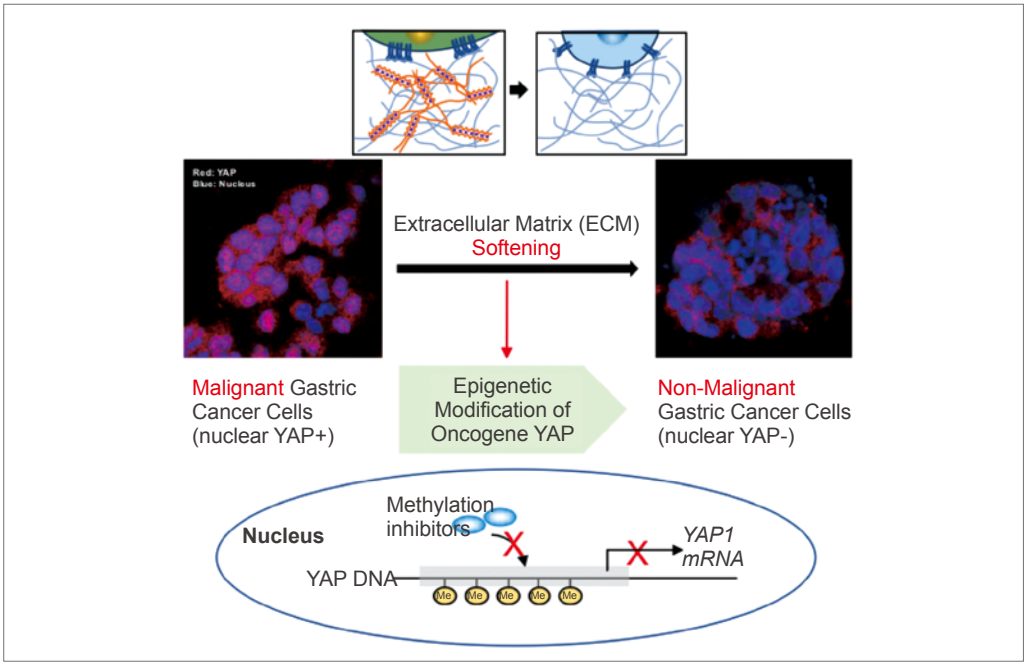
2. Contents

To investigate matrix stiffness-induced mechanotransduction at the epigenetic level, we studied gastric cancer cells. Gastric cancer (GC) is one of the leading causes of death in East Asia, and GC incidence is rising among younger generations of adults. Extracellular matrix (ECM) density is increased in GC, and it is widely known that a stiff cancer ECM helps cancer cells proliferate and invade into nearby tissues; consequently, stiff tumor microenvironments correlate to a worse prognosis and decreased life expectancy.

In order to confirm matrix stiffness-induced mechanotransduction, we constructed collagen and interpenetrating polymer network (IPN)-based 3D gel matrices, embedded with gastric cancer cells, to recapitulate the tumor microenvironment. The stiff matrix (IPN) induced YAP activation and promoted a mesenchymal phenotype of gastric cancer cells. The YAP expression increasingly deactivated with time after matrix softening (Figure 1). Total YAP expression was also reduced, indicating that lower

transcriptional activity may epigenetically reduce total YAP gene expression. DNA hypomethylation of YAP induced by a stiff matrix can be reversed by softening the matrix. The methylation index of YAP DNA recovered with time after matrix softening. Transcriptome analysis by bulk RNA sequencing and Chromatin Immunoprecipitation-Atlas analysis identified DNA methylation-modifying genes that were recovered by matrix softening by comparing control and YAP-depleted cells. siRNA treatments of 3 genes (GRHL2, TET2, and KMT2A) confirmed the recovery of YAP DNA methylation comparable to the soft control.

Upon a proliferation and drug resistance analysis, GC cells in the softened matrix were less proliferative and less resistant to drugs than those in the stiff matrix, confirming that the softening was effective in suppressing malignancy. These findings suggest that mechanotherapy to soften tumor tissues and surrounding ECM may be an appropriate addition along with chemotherapy for better patient prognosis.



3. Expected effects

Clinically, it is important to identify potential therapeutic vulnerabilities in ECM-mediated tumour progression because tumours such as scirrhous gastric cancer harbour the poorest prognosis while few therapies are available. DNA methylation is known to be reversible, similar to other biochemical and physiological modifications, and is thus regarded as a promising target for therapeutic interventions. In this respect, our findings offer insight into promising mechanotherapeutic strategies specifically targeting the mechanical properties of the ECM, to regulate the epigenetic status and oncogenic transcription activity of malignant tumour cells.

Research outcomes

[Paper] M. Jang, J. An, S. W. Oh, J. Y. Lim, J. Kim, J. K. Choi*, J.-H. Cheong*, P. Kim*, "Matrix stiffness epigenetically regulates the oncogenic activation of the Yes-associated protein in gastric cancer", Nature Biomedical Engineering, (2020) [2020 IF: 18.952]

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