

# Role of epigenetic modifications in the establishment of mechanical memory

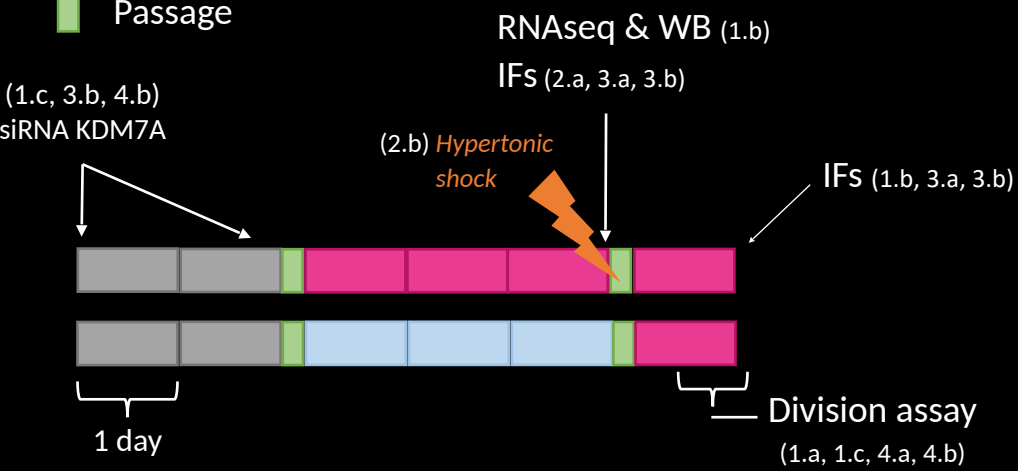
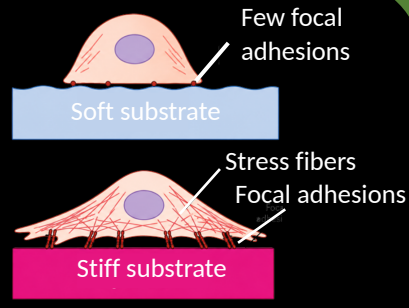
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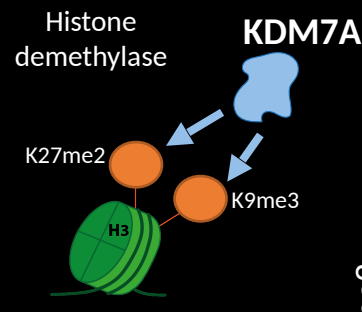
Mechanical memory is defined by the persistent effect of past environment rigidity on cell adaptation to a new environment. Different mechano-sensitive signaling pathways have been implicated in mechanical memory. However, it is currently unknown how past information about substrate stiffness is stored inside the cell. Here, we report that the histone demethylase KDM7a controls mechanical memory of cell division by regulating H3K27 demethylation in a nuclear membrane tension-dependent manner. We observed that KDM7a was overexpressed in cells cultured on a soft substrate and was required to encode memory of a past soft substrate. On soft environments, reduced nuclear membrane tension controlled KDM7a recruitment at the nuclear envelop and H3K27 demethylation. Conversely, KDM7a localized to the nucleoplasm on stiff environments and H3K27 was methylated. These differences of histone methylation was maintained once cells primed on a soft substrate were transferred to a stiff secondary environment. Manipulation of nuclear membrane tension revealed that KDM7a localization was controlled by tension. We propose that information about substrate rigidity is encoded and stored in the epigenome through nuclear membrane tension-regulated H3K27 methylation dynamics.

## Experimental protocol

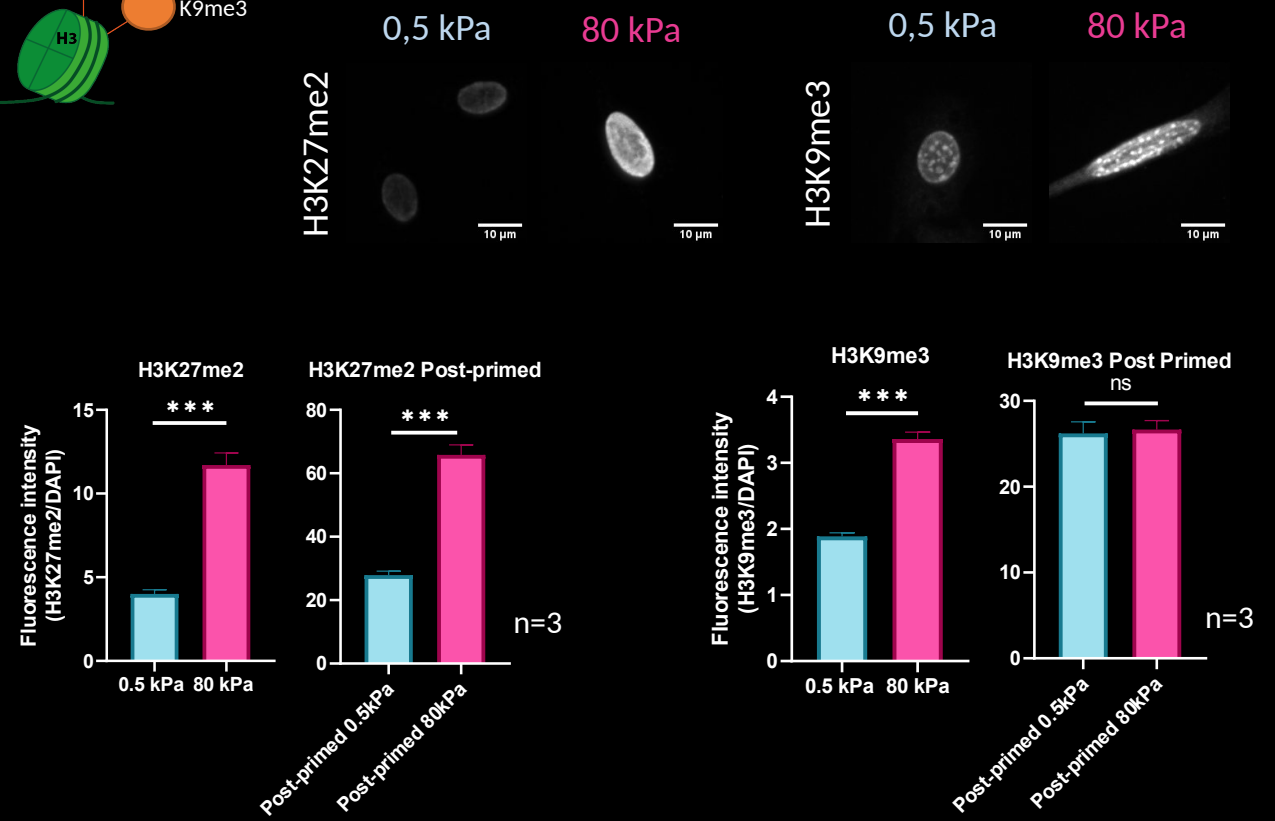
- Plastic
- 80kPa = stiff substrate
- 0,5kPa = soft substrate
- Passage



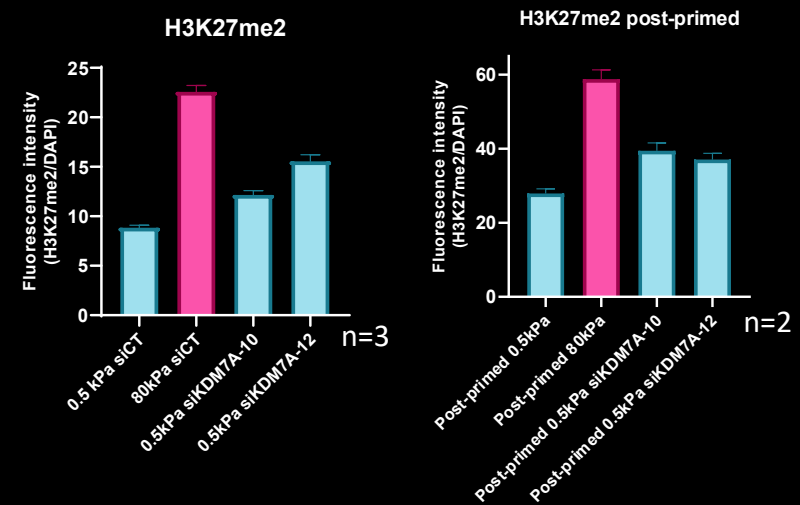
## 3 Mechanical memory is encoded by H3 demethylations



a- H3K27 demethylation state is maintained after replating



b- Depletion of KDM7a partially rescues H3K27me2 intensity and is maintained after replating



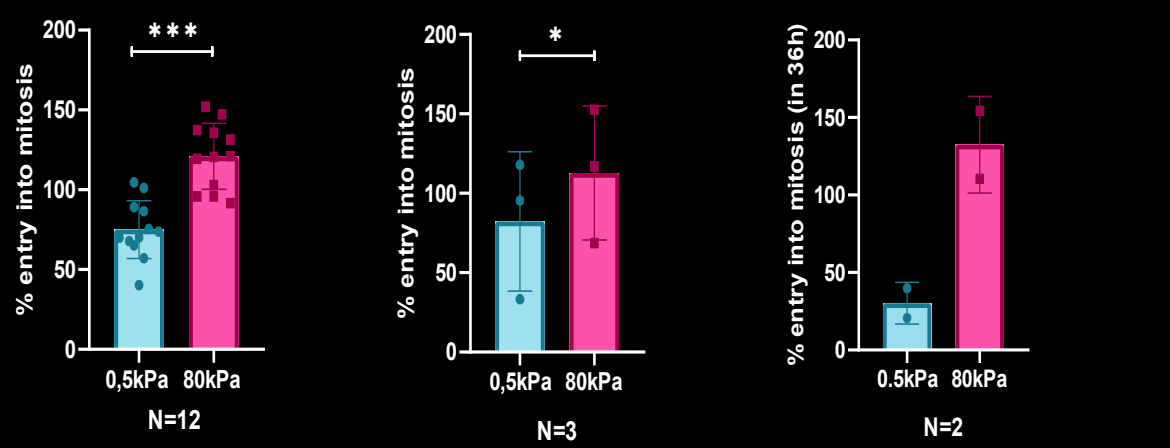
## 1 KDM7A : a demethylase involved in the acquisition of the mechanical memory

a- Cells are able to acquire a mechanical memory

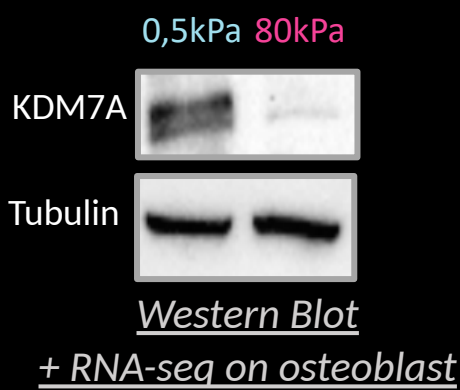
Osteoblast

HS578T

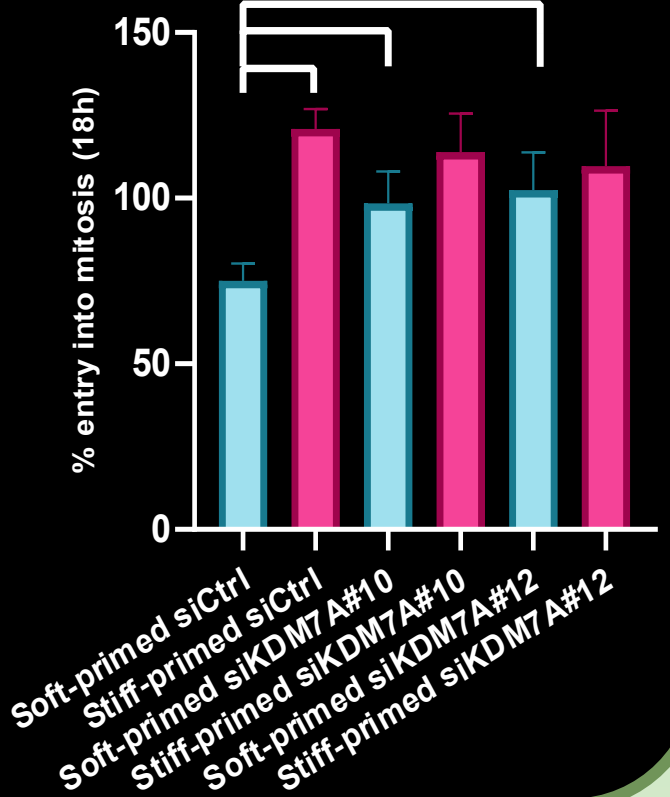
RPE1



b- KDM7A is overexpressed on soft substrate

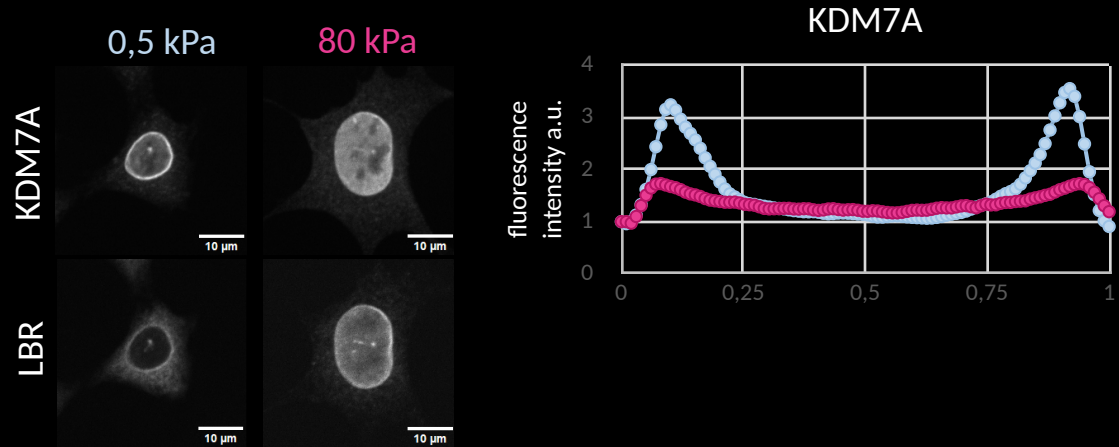


c- Depletion of KDM7A rescues cell division

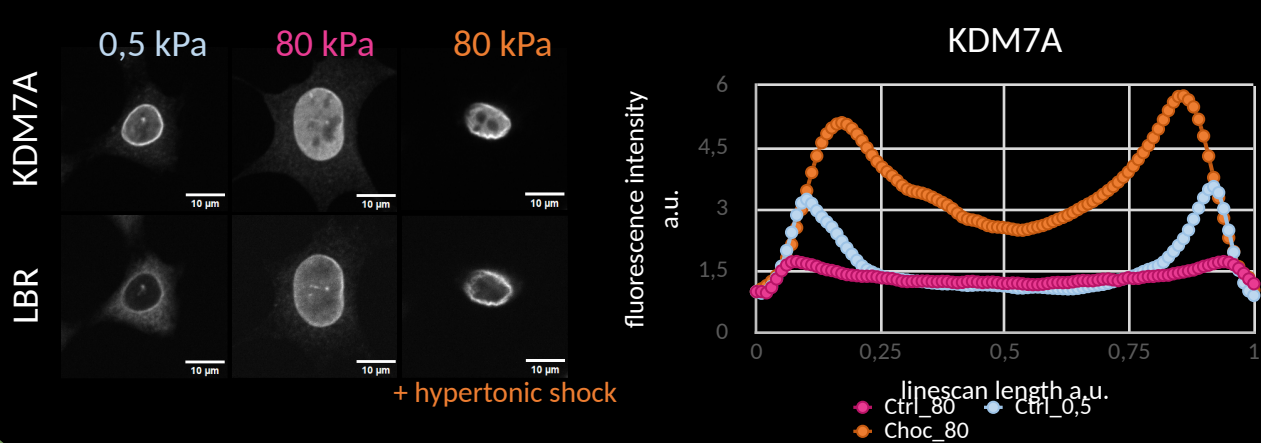


## 2 KDM7A localisation depends on nuclear tension

a- KDM7A is localized at the nuclear envelop on soft substrate

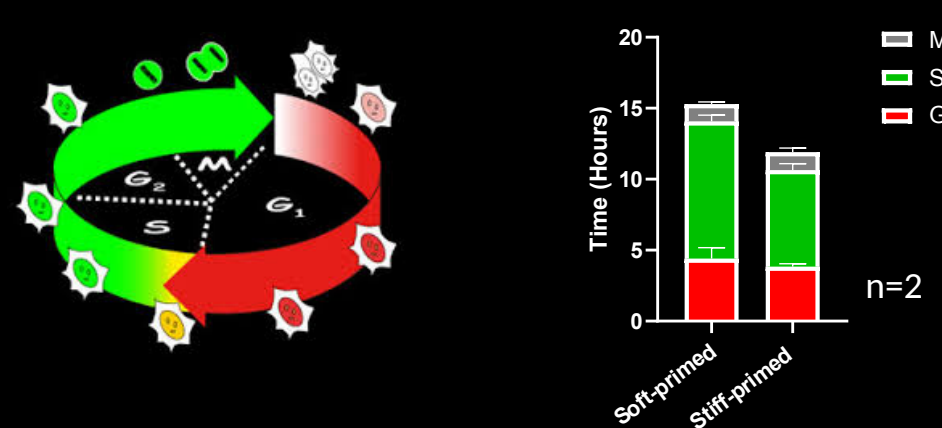


b- A decrease in nuclear tension induces a recruitment of KDM7A at the nuclear envelop

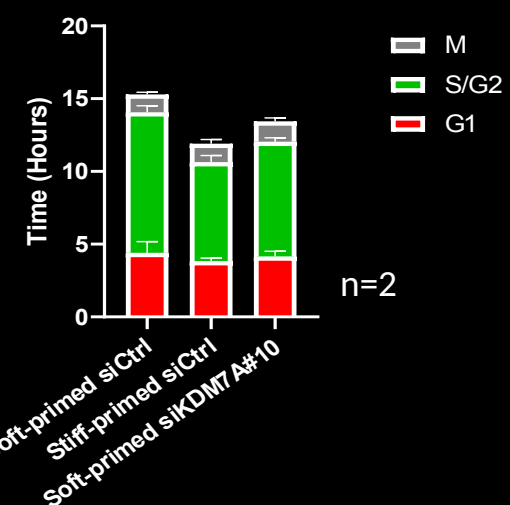


## 4 KDM7A affects S/G2 phase of the cell cycle

a- G2/S phase is slowed down in soft-primed cells



b- Depletion of KDM7a partially rescues S/G2 phase



## Proposed model



KDM7a is an epigenetic modulator which prints mechanical memory of the division through H3K27me2. These epigenetic modifications lead to the activation of genes involved in S/G2 phase control or mitosis delay to print mechanical memory of the division