The point of no return: Chromatin enforces cell fate decisions

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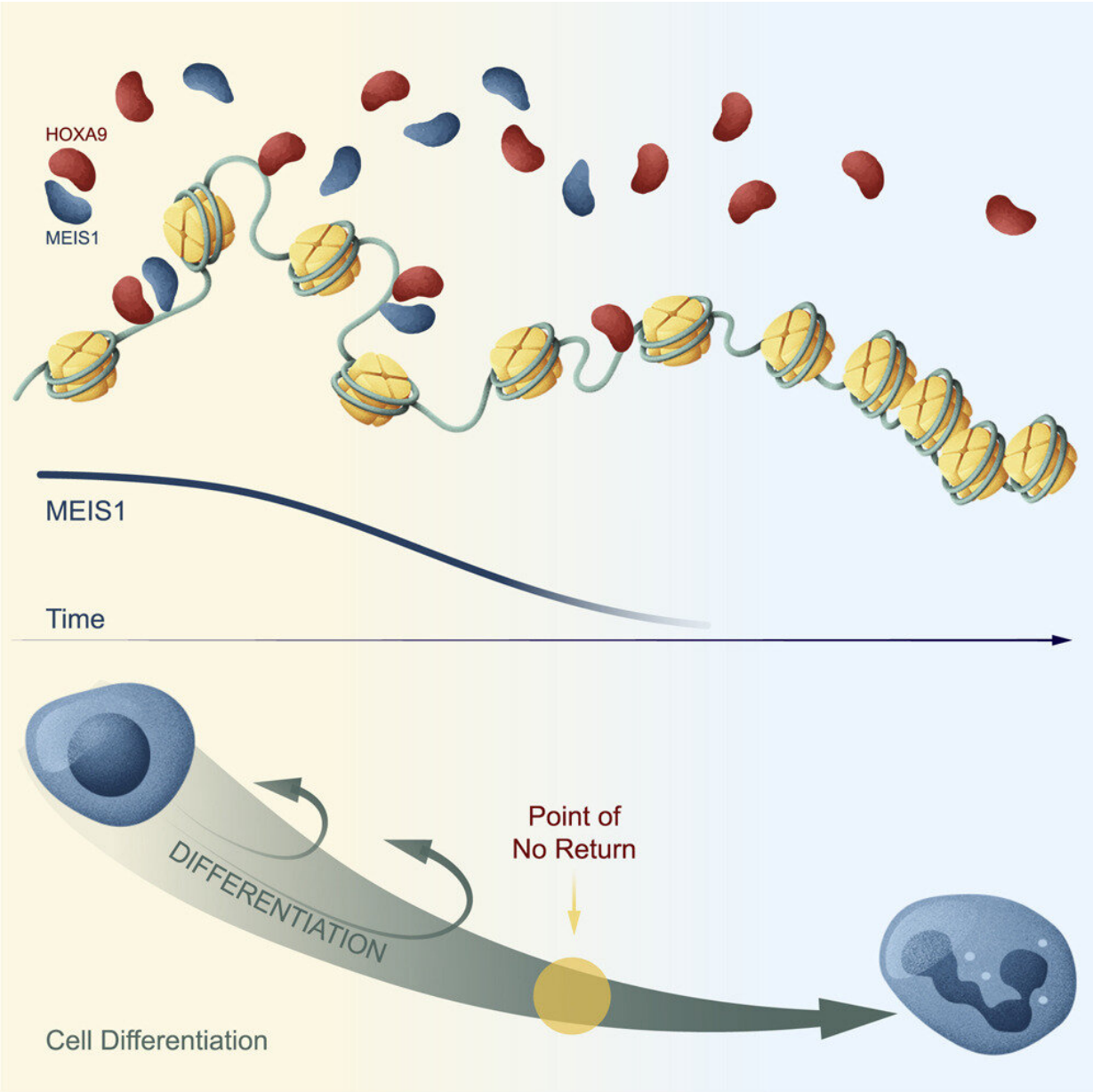

Graphical abstract. Credit: DOI: 10.1016/j.celrep.2021.109967

Stem cells balance self-renewal with differentiation into mature cells. A fundamental and intriguing question is when during the process of maturation a cell reaches a "point of no return," losing its capacity to self-renew and becoming committed to differentiating into a specific cell type.

Ludwig Oxford's Yang Shi and his former postdoc Andres Blanco, who is now at the University of Pennsylvania, led a study on the induction of that commitment in blood stem cells known as hematopoietic myeloid progenitors. In a study published in *Cell Reports*, they and their colleagues show that the chromatin environment on DNA—the combination of DNA and histone proteins—plays a key role enforcing cell fate decisions.

The researchers studied the production of terminally differentiated neutrophil white blood cells from myeloid stem cells and found that a combination of remodeling of chromatin structure, activation of gene control elements (enhancers) and changes in transcription factor usage contribute to an irreversible commitment to differentiation. These changes result in reduced accessibility to regulatory DNA sites and disruption of a positive feedback transcription factor activation loop that prevents differentiation.

This greater understanding of the biological mechanisms involved in the production of mature blood cells from blood stem cells could aid strategies to manipulate this process for such purposes as tissue regeneration or cancer therapy. The new findings have relevance for acute myeloid leukemia (AML), in which differentiation is arrested. By helping to define the molecular processes involved in differentiation,

this study aims to identify targets against which to develop new AML differentiation therapies.

More information: M. Andrés Blanco et al, Chromatin-state barriers enforce an irreversible mammalian cell fate decision, *Cell Reports* (2021). DOI: 10.1016/j.celrep.2021.109967

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