Short-term treatment with retinoic acid prevents spontaneous differentiation of murine embryonic stem cells

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Murine embryonic stem cells (ESCs) self-renew indefinitely while maintaining the ability to generate all three germ-layer derivatives. These cells undergo spontaneous differentiation process in the absence of leukemia inhibitory factor (LIF) and feeder cell layer. Previous study revealed that cellular factors such as LIF from differentiating ESCs can inhibit subsequent differentiation, suggesting a feedback regulation of ESC self-renewal from differentiating cells. However, the molecular mechanism underlying such regulation is poorly understood. Retinoic acid (RA), a derivative of vitamin A, has been well documented to play critical roles in mESC differentiation and embryogenesis. Here we reported a new role of RA in self-renewal of mESCs via a feedback regulatory mechanism. We demonstrated that RA treatment during the early stage of differentiation maintained self-renewal of mESCs and sustained expression of the pluripotent state-specific transcription factors Oct-4 and Nanog. These ESCs remained undifferentiated state and retained the potential to differentiate spontaneously. We then identified the cellular factors and the regulatory pathways responsible for such effect of RA. These findings provide new insight into the function of RA in regulation of ESC commitment.

Keywords: murine embryonic stem cells, retinoic acid, differentiation, self-renewal, LIF

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