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5-azacytidine reactivates pluripotency gene expression, affects TET2 and histone transcription and modifies chromatin organization and morphology of mammal skin fibroblasts.

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Abstract

Phenotype expression is controlled by epigenetic regulations that guide cells through differentiation. The process is reversible and cells can be driven back to a higher plasticity state with the use of epigenetic modifiers. In this work we exposed skin fibroblasts to the demethylating agent 5-azacytidine (5-aza-CR), which is a well-known DNA methyltransferase inhibitor, and has been recently shown to increase cell plasticity and facilitate phenotype changes in different cell types (Pennarossa, 2013; Brevini, 2014; Pennarossa, 2014; Brevini, 2016). Although many aspects controlling its demethylating action have been widely investigated, the mechanisms through which 5-aza-CR acts on cell plasticity are still poorly understood. At the end of 5-aza-CR treatment, cells were divided in three experimental groups and cultured for 24 and 48 hours: A) cells were returned in standard fibroblast medium; B) cells were cultured in medium specific for pluripotency maintenance; C) cells were placed in a medium encouraging pancreatic differentiation. At the end of the culture period, as expected, we could observe a global demethylating effect. In parallel, however we detected a transient upregulation of the pluripotency genes OCT4, NANOG and REX1. Increased transcription of TET2 and histones belonging to the 1,2,3 and 4 families, together with changes in the expression of enzymes controlling histone acetylation were also appreciated. Interestingly, these results were accompanied by morphological and ultrastructural changes as well as by chromatin structure modifications. All together our findings indicate that 5-aza-CR induced somatic cell transition to a higher plasticity state involves novel cellular targets that activate multiple epigenetic regulatory pathways.

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