Editorial

Stem Cell INVESTIGATION

The RNA helicase DDX5 is a reprogramming roadblock

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The reprogramming of somatic cells into induced pluripotent stem cells (iPSCs) is a major challenge for medical applications such as regenerative medicine since iPSCs can be used to generate different types of functional differentiated cells. Up to now, strategies aiming at reprogramming somatic cells have been mainly conducted toward the targeting of factors modifying gene expression at the transcriptional level. However, gene expression is a multistep process involving epigenetic and transcriptional regulators, as well as RNA binding proteins and miRNAs regulating mRNA splicing, stability or translation. The different steps of the gene expression process are physically, spatially and temporally interconnected, and each factor involved in this process may itself be controlled by other regulators within that chain of molecular mechanisms. Therefore, understanding the interplay between the different gene expression layers during cell differentiation and cell reprogramming is expected to improve strategies aiming at producing both pluripotent stem cell and differentiated cells.

In this context, Huanhuan Li and collaborators (1) have recently identified the DEAD box RNA helicase DDX5 as a major barrier to somatic cell reprogramming. In their paper, they demonstrate that DDX5 plays a major role in the processing of miR-125b that in turn represses the expression level of the RING1 and YY1 Binding Protein (RYBP). RYBP is shown to induce pluripotency-associated genes while it represses the expression of development-specific genes. More precisely, the authors demonstrate that RYBP interacts with OCT4 and that the depletion of RYBP reduces the binding of OCT4 to the Kdm2b promoter. Collectively, the work from Huanhuan Li and collaborators suggests that RYBP is involved in the regulation of OCT4-dependent pluripotency gene network. Huanhuan Li and collaborators also show that RYBP promotes the H2AK119ub1 repressive chromatin marks as part of the non-canonical PRC1 complex on the promoters of a set of developmental genes.

The paper by Huanhuan Li and collaborators adds a new string to the bow of DDX5, which appears to be at the heart of various molecular pathways controlling cell fate decisions. Whether this protein (or its highly-related paralog DDX17) regulates the activity of a cell-specific transcription factor, the expression of master differentiation miRNAs, or the switch between alternative splicing isoforms (2), all the functions assigned so far to these RNA helicases make them essential players in various differentiation processes or biological transitions.

The study by Huanhuan Li and collaborators (1) clearly demonstrates that manipulating the expression or activity of regulators other than epigenetic and transcriptional regulators (e.g., RNA binding proteins, miRNAs) may open new promising avenues toward the establishment of more efficient and maybe safer strategies aiming at producing iPSCs. In particular, there is an increasing interest in targeting RNA binding proteins since post-transcriptional regulation plays a major role in both cell differentiation and cell reprogramming (3). Of particular

interest, DDX5 and other similar RNA helicases are promising candidates because of their involvement in different steps of the gene expression process (2). By taking advantage of their specific enzymatic activity (i.e., ATP-dependent helicase), it might also be possible to target them using small molecules to pharmacologically control cell reprogramming or differentiation (4). However, this will first require to understand at the molecular level how these proteins control each step of the gene expression process. It is interesting to underline that Huanhuan Li and collaborators have observed that DDX5 does not only control the expression level of RYBP in a miRNA-depending manner, but that the RNA helicase is also part of a RYBP-containing complex that is probably involved in transcription regulation. Even though the authors did not specifically address the consequences of this interaction for RYBP-mediated effects, it will be interesting in the future to better characterize this interplay between DDX5 and RYBP. Along the same line, even though DDX5 appears to be a barrier for somatic cell reprogramming, its expression is upregulated during this process (1). It would be interesting to look for potential post-translational modifications that could direct DDX5 toward different complexes involved in the regulation of different sets of genes (e.g., pluripotency-associated *vs.* development-specific genes) or involved in different molecular processes (e.g., transcription *vs.* miRNA processing). Doing so, it will be possible to better understand the cellular pathways and signaling cascades that could be pharmacologically modulated to achieve efficient cell differentiation or cell reprogramming.

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Footnote

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