Hierarchical mechanisms for direct reprogramming of fibroblasts to neurons.

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Public Summary:
The conversion of readily available cell types, such as skin cells, into therapeutically relevant cells (i.e. neurons, cardiomyocytes) is a promising approach for generating material which can be used to test new therapeutic compounds and to study human disease in the lab. In this paper, we investigated the mechanisms that underlie the conversion of skin cells into functional neurons, which is accomplished by forced expression of three neuronal genes (called Ascl1, Brn2, Myt1l) in the skin cells. We performed these experiments because we believe that a detailed understanding of the mechanisms that underlie this fate conversion will help to improve the efficiency and fidelity of the conversion process, making it a more facile tool for studying human biology. We discovered a unique signature in the chromatin of the host cells (i.e. skin cells) that helps to predict whether or not they can successfully be reprogrammed by this method. We also identified another gene, Zfp238, that is a novel regulator of cellular reprogramming. Thus, using a variety of state-of-the-art approaches enabled by high-throughput DNA sequencing technologies, we have elucidated important new features that will help to improve currently available methods for reprogramming skin cells into neurons.

Scientific Abstract:
Direct lineage reprogramming is a promising approach for human disease modeling and regenerative medicine, with poorly understood mechanisms. Here, we reveal a hierarchical mechanism in the direct conversion of fibroblasts into induced neuronal (iN) cells mediated by the transcription factors Ascl1, Brn2, and Myt1l. Ascl1 acts as an "on-target" pioneer factor by immediately occupying most cognate genomic sites in fibroblasts. In contrast, Brn2 and Myt1l do not access fibroblast chromatin productively on their own; instead, Ascl1 recruits Brn2 to Ascl1 sites genome wide. A unique trivalent chromatin signature in the host cells predicts the permissiveness for Ascl1 pioneering activity among different cell types. Finally, we identified Zfp238 as a key Ascl1 target gene that can partially substitute for Ascl1 during iN cell reprogramming. Thus, a precise match between pioneer factors and the chromatin context at key target genes is determinative for transdifferentiation to neurons and likely other cell types.