Reprogramming of human fibroblasts into multipotent cells with a single ECM proteoglycan, fibromodulin.

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Public Summary:
The potential application of stem cells in regenerative medicine is increasingly promising especially in defects that are difficult to be self-regenerate. However, obtaining a safe, reliable and sufficient source of stem cell for such treatment is a major limitation and challenge in tissue engineering. The principle challenge today is to produce enough regenerative cells through a simple, consistent process that bypasses ethical and immunological barriers and avoids genome alteration for in vivo skeletal muscle and bone construction without causing tumor formation. In this manuscript, we established a novel, safe multipotent cell generation technique called fibromodulin (FMOD) reprogramming integrates three areas of innovation to achieve this goal: [1] technical innovation – we have established a simple and yet revolutionary approach to obtain multipotent cells from somatic cells using a single extracellular matrix (ECM) proteoglycan, FMOD, which is the very first known method that uses a single molecule to reprogram somatic cells; [2] biological innovation – unlike unreliable induced pluripotent stem cell (iPSC) generation, FMOD reprogramming does not require genome integration; and [3] therapeutic innovation – FMOD reprogrammed (FReP) multipotent cells can be easily differentiated into skeletal myocytes and osteoblasts in vitro and in vivo, respectively, and will have significant clinical value in regenerative medicine to establish skeletal muscle and bone by autologous cells. Since FMOD reprogramming clearly involves neither oncogenes nor genome integrative approaches and FReP cells do not generate teratoma in vivo, FMOD reprogramming fulfills the requirements of the FDA to produce safe multipotent cells without known undesirable side effects. Therefore, FMOD reprogramming provides an alternative strategy for engineering patient-specific multipotent cells for basic research and therapeutic application.

Scientific Abstract:
Pluripotent and/or multipotent stem cell-based therapeutics are a vital component of tissue engineering and regenerative medicine. The generation or isolation of safer and readily available stem cell sources will significantly aid clinical applications. We report here a technique using a single molecule, recombinant human fibromodulin protein (FMOD), to reprogram human fibroblasts into multipotent cells. Like virally-induced pluripotent stem (iPS) cells, FMOD reprogrammed (FReP) cells express pluripotency markers, form embryoid bodies (EBs), and differentiate into ectoderm, mesoderm, and endoderm derivatives in vitro. Notably, FReP cells regenerate muscle and bone tissues but do not generate teratomas in vivo. Unlike iPS cells, undifferentiated FReP cells proliferate slowly and express low proto-oncogene c-MYC and unexpectedly high levels of cyclin-dependent kinase inhibitors p15(Ink4B) and p21(WAF1/Cip1). Remarkably, in a fashion reminiscent of quiescent stem cells, the slow replicative phenotype of undifferentiated FReP cells reverses after differentiation induction, with differentiating FReP cells proliferating faster and expressing less p15(Ink4B) and p21(WAF1/Cip1) than differentiating iPS cells. Overall, single protein, FMOD-based, cell reprograming bypasses the risks of mutation, gene instability, and malignancy associated with genetically-modified iPS cells, and provides an alternative strategy for engineering patient-specific multipotent cells for basic research and therapeutic application.