Identification of a population of quiescent pluripotent stem cells within peripheral nerves

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Evidence from our laboratory has documented a large population of quiescent stem cells within peripheral nerves. In response to nerve injury, or stimulation with the cytokines (eg BMP2), these cells proliferate and generate populations of pluripotent stem cells, expressing Sox2, Klf4, Oct4 and c-Myc (verified by double stain immunohistochemistry and by real time PCR). These 4 markers are the transcription factors that confer embryonic pluripotency (Cell 126: 663, 2006). We call them nerve derived pluripotent stem cells, or NEDAPS cells. The cells propagate well in restrictive media and are readily induced to form tissues from all 3 germ layers. We hypothesize that pluripotent stem cells are indeed residing in peripheral nerves and they represent the central feature in an important and previously unknown universal pathway for tissue repair. Nerves are nearly ubiquitous in the body, from the cornea of the eye to every hair follicle. Thus, we believe that nerve injury and the consequent proliferation of these stem cells, occurs following essentially any injury. The cell of origin for these pluripotent stem cells are the Schwann cells, which have long been known to have remarkable plasticity, demonstrated by their behavior after a nerve transection. We believe that we have uncovered a previously unknown universal pathway for healing.

We will show data documenting the induction and successful culture of these unique new pluripotent cells from three mammalian species, mouse, rat and human and demonstrate their directed differentiation into osteoblasts, endothelial cells, primitive nerve cells, definitive endoderm, brown fat and fibroblasts as demonstrated by morphology, immunohistochemical staining and by real time polymerase chain reaction (RT-PCR) data to document cell specific gene expression.

Stem cell biology is a field that has recently seen an explosion of new work. stimulated by Dr Yamanaka's remarkable discovery that induced pluripotent stem cells (iPCs), or cells capable of differentiating into any cell type, could be created from fully differentiated cells by forcing expression of the genes for only 4 transcription factors (listed above), most often by the use of retrovirus vectors (Cell 126: 663,2006). Such iPCs are being widely studied as possible sources of cells for the treatment of human disease. This work has been hampered by issues of malignant transformation of iPCs and by immune rejection of these "non-self" cells. Previous claims to successful identification of cells with universal differentiation from non-gonadal adult tissue have sadly resulted in some notable and well publicized scandals, involving fabricated data). These scandals have understandably created a skeptical audience for us. Such pluripotent stem cells are thought not to exist in adult animals (SciON 311: 814 2006) and until the recent discovery of these cells by our group, we believed the same.

We propose that this new knowledge will also explain the puzzling and vexing clinical problem of impaired wound healing experienced by severely diabetic patients and victims of leprosy. We suggest that in the severe depletion or absence of Schwann cells due to the severe neuropathies caused by these illnesses, essentially makes wound healing impossible. The other implication of this discovery is that we may now have a straightforward opportunity to obtain individual specific "self-to-self" stem cell treatments based on a minimally invasive biopsy of a nonessential peripheral neve of a specific patient in need, from which NEDAPS cells could be easily propagated *ex vivo*. These NEDAPS cells could be differentiated into cells specifically needed by the individual patient who provided the nerve tissue. We suspect that this scheme will bypass the risk of malignant transformation, as well as immune rejection. This method has been successfully applied to a skin healing model, as well as fracture healing models.

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