Understanding Neurogenesis in the Subventricular Zone and the Capacity for Transcriptional Modulation in Ischemic Brain Injury

Isaac Josh Abecassis[1] *and Michael R. Levitt*[1-3]

Neural stem cells (NSCs) are endogenously produced in the hypothalamus,[1] the subventricular zone (SVZ) of the lateral ventricles,[2] and the dentate gyrus of the hippocampus.[3] Neurogenesis in the SVZ has been well characterized; activation produces a "stream" of neuroblasts that migrate along the rostral migratory stream (RMS) to the olfactory bulb, ultimately destined to enhance cortical plasticity via integration into existing functional circuits as interneurons.[4] This RMS occurs within a tube of supporting glial cells, and the process seems to be activated with brain injuries.[5] There are 4 types of cells present in the SVZ, including neuroblasts (type-A cells), NSCs (with a subtype B1 and B2 cells), transit amplifying progenitors (TAPs, or type-C cells), and ciliated ependymal cells (type E cells) (Figure 1).[6,7] There has been tremendous interest in defining the molecular landscape of this process, yielding the valuable identification of key transcription factors and protein families intimately involved in neurogenesis, like the forkhead box (Fox) proteins—a group of transcription factors with signaling pathways clearly associated with NSC homeostasis and pathologic tumorigenesis.[7,8] In fact, this SVZ NSC population has been described in

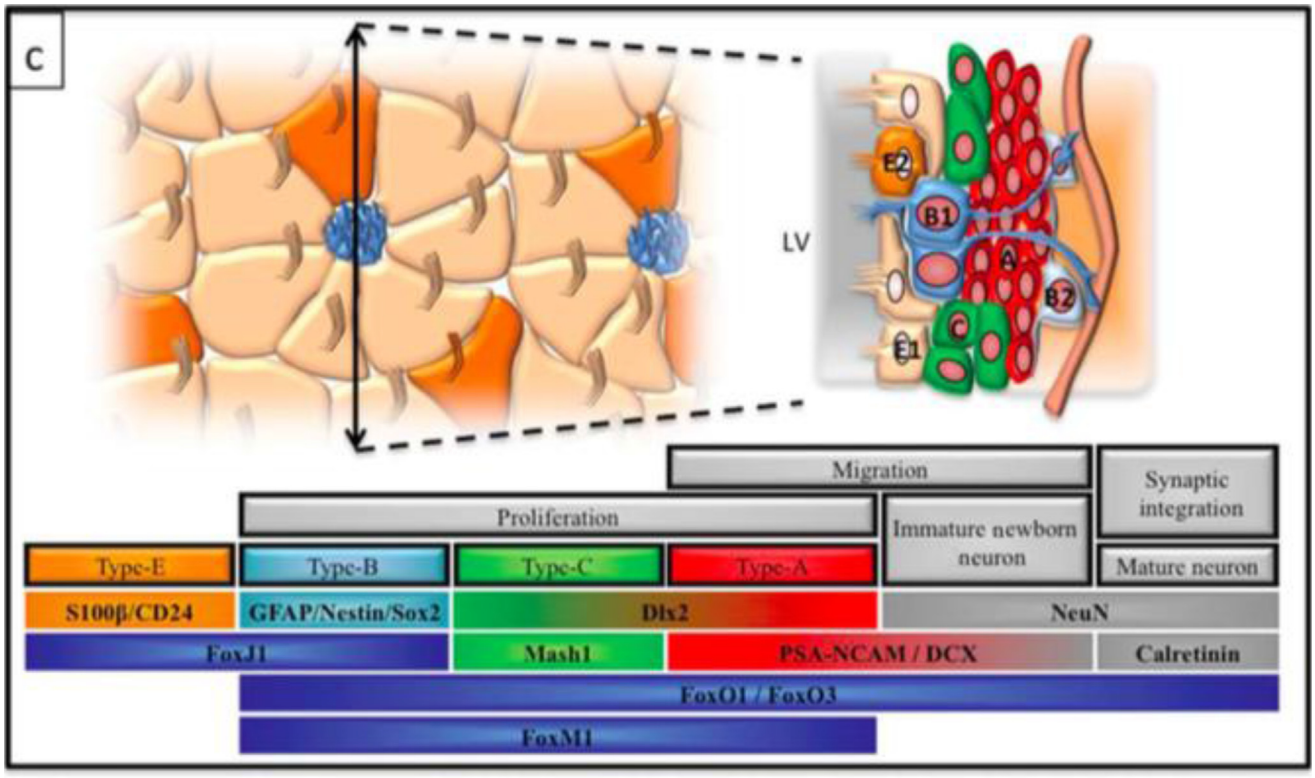

Figure 1. Visual representation of the subventricular zone (SVZ), with the various key cell types involved including ependymal cells (type E1 and E2 cells), neural stem cells (NSCs, types B1 and B2), neuroblasts (type A cells), and transit amplifying progenitors (TAPs, or type-C cells). Also labeled on the bottom are key forkhead box (Fox) proteins implicated in various stages of neurogenesis. From Genin EC, Caron N, Vandenbosch R, Nguyen L, Malgrange B. Concise review: forkhead pathway in the control of adult neurogenesis. *Stem Cells*. 2014;32:1398-1407.

some reports as the culprit for primary brain tumors, under the premise that a deranged stem cell biology produces tumor.[9,10] Additionally, this endogenous stem cell population is activated with hypoxic brain injuries, so there is some hope that potentially modulating this process may contribute to better neurological recoveries in specific disease states.[11] Yet the details involved with selecting for specific cellular identities remains murky. In their recent report in *Cell Stem Cell*, Llorens-Bobadilla et al.[12] elucidate

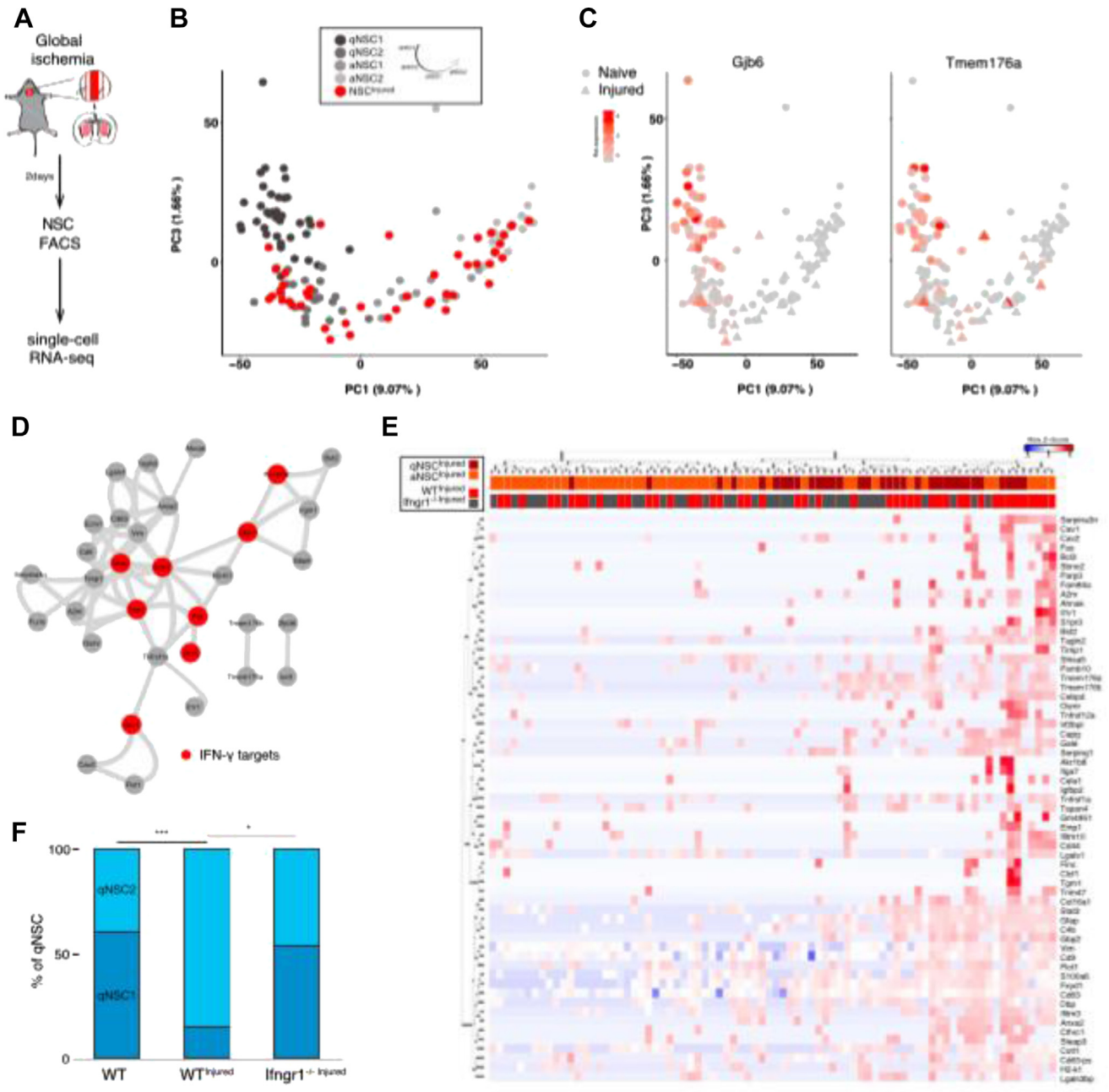

Figure 2. Interferon-gamma (IFN-γ) signaling as the mechanism for neural stem cell (NSC) activation after ischemic brain injury. (**A**) Experimental design. (**B**) Transcriptional analysis showing more active subpopulations of NSCs in an injured state (*red dots* indicate injured NSCs). (**C**) Relative gene expression levels for 2 sample genes from a list that comprise the "injury signature." (**D**) Selected genes that are strongly expressed in injury signature. *Red dots* connote genes that were predicted to be IFN-γ targets based on an upstream regulatory analysis. (**E**) Heat map for gene expression of 61 genes in NSCs; columns indicate whether the cells are from wild-type (WT) animals or transgenic ones. (**F**) Relative proportion of cells within qNSC for WT, WT injured, and transgenic injured cells.