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**Title: AGE ASSOCIATED INDUCTION OF SENESCENT TRANSCRIPTIONAL PROGRAMS IN HUMAN GLIAL PROGENITOR CELLS**

**Abstract:**

Glial progenitor cells, a primary source of oligodendrocytes and astrocytes in the human CNS, emerge during the 2nd trimester to colonize the brain, in which a parenchymal pool remains throughout adulthood. While fetal human GPCs (hGPCs) are highly migratory and proliferative, their expansion competence and phenotypic potential may diminish with aging, as well as following demyelination-associated turnover. To determine the basis for this age-related decline in the mobilization capacity of hGPCs, we used both bulk and single cell RNA-Sequencing to compare the transcriptional programs of fetal and adult hGPCs. We identified age-associated changes in gene expression suggesting a loss of proliferative competence with aging, concurrent with the onset of both differentiation and senescence-associated transcriptional programs. Whereas the maintenance of the fetal glial progenitor state was associated with enrichment of the transcriptional activators MYC, NFIB, HMGA2 and TEAD2, and the repressors BCL11A, EZH2 and HDAC2, the maturation of adult hGPCs was associated with the concurrent appearance of the transcriptional activator STAT3, and the repressors ZNF274, MAX, E2F6, and IKZF3. Individual over-expression of each of these adult transcriptional repressors in human iPSC-derived GPCs, which otherwise express a fetal-like transcriptional signature, led to a loss of proliferative gene expression and an induction of markers of senescence, which replicated the transcriptional changes incurred during glial aging. We then coupled these transcriptional data with miRNA profiling of fetal and adult hGPCs, which identified an adult-selective miRNA expression signature whose targets may further constrain the expansion competence of aged GPCs. These observations indicate that the aging of hGPCs proceeds through the acquisition of a MYC-repressive environment, and suggest that the suppression of age-associated repressors of glial expansion may permit the rejuvenation of aged hGPCs.