

**96th Annual Meeting**  
**April 16-20, 2005**  
**Anaheim/Orange County, CA**

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**Abstract Number:** 1065  
**Presentation Title:** Id2 and Id4 expression and function in glioblastoma multiforme and neural stem cells  
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**Author Block:** *Kyuson Yun, Paula Knittle, Akio Mantani, Mark A. Israel.* Dartmouth Medical School, Norris Cotton Cancer Center, Hanover, NH, Hiroshima University, Hiroshima, Japan

Helix-loop-helix (HLH) proteins regulate proliferation and differentiation in both developing mouse embryos and in human tumor-derived cell lines. We found that Id4 and Id2 are highly expressed in high-grade brain tumor tissues and some brain tumor-derived cell lines, but only at very low levels in normal mature brain tissue. As a prelude to studying the role of these important genes in the biology of brain tumors, we examined their function in vivo, analyzing the brains of Id4<sup>-/-</sup>; Id2<sup>-/-</sup>, Id4<sup>-/-</sup>; and Nestin-Id2 transgenic animals. Consistent with the known role of Id genes to inhibit differentiation and promote proliferation, Id4<sup>-/-</sup> embryos have smaller brains and this phenotype arises from both premature differentiation and defective G1-S transition in early neural stem cells. Importantly, this phenotype is more severe in the dorsal medial cortex and hippocampus suggesting either that other Id genes compensate for Id4 in the lateral cortex or that in different regions of the brain, there are environmental influences that can modify the effect of genetic alterations that regulate brain maturation. The Id2 single null animal does not show an obvious brain phenotype, and the Id2/4 double null brain phenotype is similar to that of the Id4 single null animal, indicating that Id2 is not compensating for Id4 in the lateral cortex. Surprisingly, in contrast to in vitro studies showing that ectopic expression of Id2 inhibits differentiation and promotes proliferation, ectopic expression of Id2 from the Nestin promoter in neural stem cells leads to a smaller, rather than a larger, brain phenotype in vivo. This phenotype results from both reduced lateral expansion of the neuroepithelium (approximately 30% at E12.5) and increased apoptosis (greater than 10 fold at E12.5), providing in vivo evidence for the role of Id2 in inducing apoptosis and implicating Id2 in regulating neural stem cell maintenance, proliferation, and maturation. Furthermore, while both mutant brains show compromised lateral expansion of the neuroepithelium, there is no increased apoptosis in Id4<sup>-/-</sup> animals. Together, the similarities and differences between Id4<sup>-/-</sup> and Nestin-Id2 transgenic animals suggest that Id2 and Id4 affect both overlapping and unique pathways in neural stem cells. We are currently testing the effects of Id2 and Id4 expression in brain tumor derived cell lines by both gain- and loss-of-function approaches. In addition, we are examining the molecular mechanisms underlying the apparently opposing functions of Id2 and Id4 by identifying downstream target genes of Id4 and analyzing the pathways that Id4 and its target genes regulate in human brain tumor-derived cells.

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