

DR PINTAR 12/28/03
01.3012.OCR.5.0
FINAL NARRATIVE

A. Summary of progress

The major goals of the project were to assess the role of IGFBP-5 in known models of cell death and to determine if the absence of BP-5, which is expressed in early stages of motor neuron differentiation, leads to alteration in motor neuron number in KO mice lacking this gene. To assess the prospective role in cell death, we extended study of the effect of IGFBP-5 absence on mammary gland involution. Prior work had indirectly suggested that IGFBP-5, which is rapidly induced during involution, would promote cell death by binding IGF-I, and thus limit the effects of a known trophic factor. To test this, wild-type and IGFBP-5 female mice were examined over a ten day period following the induction of involution to assess the extent of involution as well as to assess the immunocytochemical markers of cell death. The results of this study were remarkable, and indicated a specific role of IGFBP-5 in this process. Thus, in IGFBP-5 KO mice, the extent of involution (cell death) was delayed at least three days compared to wild-type littermates with results from both morphology and caspase-3 immunostaining (a marker of cell death), as well as TUNEL analysis (another marker of cell death) showing the same delayed patterning. These data were presented and very positively received as part of an invited talk at the Gordon Conference on IGFbps in April, 2003.

These data thus indicated a prospective role for IGFBP-5 in controlling the pruning of motor neuron number that accompanies development of these cells, since early differentiating motor neurons represent another site of IGFBP-5 expression. Thus studies were conducted to assess possible alterations in motor neuron cell number in IGFBP-5 KO mice. Although our specific interest was to determine whether IGFBP-5 absence altered neuronal degeneration that normally occurs in fetal and neonatal mice, we also believed that the early expression of IGFBP-5 in motor neurons could lead to long-term changes that could alter survival of these neurons in the adult as well and thus perhaps alter responses to spinal cord injury. Cell counts of both neonatal and adult IGFBP-5 KO mice showed no difference in motor neuron cell number at either age, indicating that effects on apoptosis seen in the mammary gland do not extend to the spinal cord.

Finally, based on the relationship of IGFBP-5 to mammary gland function presented above, we began to examine whether differentiation of mammary glands in the BP-5 KO mice was altered. Again the results were quite interesting in that the extent of branching of mammary gland lobules is significantly greater in the IGFBP-5 Kos. Thus, our work established that IGFBP-5 does not appear to have a significant role in spinal cord motor neuron differentiation or survival, this protein clearly has a role in several aspects of mammary gland function.

B, Papers-None as yet as further analysis is needed.

C. Grants-None.