IRRADIATION-INDUCED INJURY TO THE JUVENILE BRAIN -ROLES OF SEX AND INFLAMMATION

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska Akademin vid Göteborgs Universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Medicinaregatan 3, Göteborg, torsdagen den 5 december kl. 13.00

av

Karolina Roughton

Fakultetsopponent:
Professor Jacob Raber
Oregon Health and Science University, Portland, USA

The thesis is based on the following papers or manuscripts:

I. Karolina Roughton, Marie Kalm, Klas Blomgren
Sex-dependent differences in behavior and hippocampal neurogenesis after irradiation to the young mouse brain
European Journal of Neuroscience (2012) 36, 2763-2772

II. Karolina Roughton, Martina Boström, Marie Kalm, Klas Blomgren
Irradiation to the young mouse brain impaired white matter growth more in females than in males
Cell Death and Disease (2013), in press

III. Karolina Roughton, Ulf Andreasson, Klas Blomgren, Marie Kalm
Lipopolysaccharide-induced inflammation aggravates irradiation-induced injury to the young mouse brain
Developmental Neuroscience (2013), Epub Aug 20

IV. Marie Kalm*, Karolina Roughton*, Klas Blomgren
Lipopolysaccharide sensitized male and female juvenile brains to ionizing radiation
Submitted manuscript
*these authors contributed equally

Göteborg, 2013

UNIVERSITY OF GOTHENBURG

IRRADIATION-INDUCED INJURY TO THE JUVENILE BRAIN -ROLES OF SEX AND INFLAMMATION

Karolina Roughton
Center for Brain Repair and Rehabilitation,
Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg,
Sweden, 2013

ABSTRACT

Radiotherapy is commonly used in the treatment of pediatric malignancies, but unfortunately it is associated with negative side effects, both long-term and short-term. Negative side effects following cranial irradiation involve intellectual impairments, where gender and age at treatment are important factors for the outcome. Younger age at diagnosis and female gender are associated with more severe late effects. We investigated sex-dependent differences in the response to cranial irradiation both acutely and long-term, in the presence or absence of lipopolysaccharide-induced inflammation.

Differences in the response to irradiation (IR) between the sexes were detected in the acute phase, for proliferation and cell death, in the hippocampus and in the corpus callosum. Looking at the long-term effects of IR we show that females display a more pronounced lack of growth in both the granule cell layer of the hippocampus as well as in the corpus callosum. We also show that females are more susceptible to IR, as judged by reduced proliferation and neurogenesis in the hippocampus, and reduced oligodendrogenesis in the corpus callosum, compared to males. At the behavior level, we show using the IntelliCage setup that learning and memory are impaired after one single dose of 8 Gy, more so in females. Female mice also display a more anxious behavior in the open field and elevated plus maze compared to their male counterparts.

Pre-treatment with LPS prior to IR reveals a sex-dependent difference, where females display a higher general inflammatory response and caspase-3-dependent cell death compared to males in the acute phase. We further show that LPS prior to IR sensitizes the brain in both male and female mice long-term. LPS-treated animals display a more pronounced lack of growth of the GCL and reduced hippocampal proliferation and neurogenesis. We also show that microglia density is highly up-regulated in the DG four months post-IR in both vehicle- and LPS-treated female mice.

In conclusion, female mice are more susceptible to IR which is consistent with clinical observations. This demonstrates that gender is an important factor to take into consideration in both the rodent and human brain. We also show that an ongoing inflammation at the time of IR aggravates the injury, which may enhance cognitive deficits in pediatric patients undergoing radiotherapy.

Keywords: Cranial radiotherapy, neurogenesis, dentate gyrus, corpus callosum, sex, inflammation, microglia, LPS, IntelliCage, open field, elevated plus maze
ISBN 978-91-628-8826-8