INFLAMMATION AND BEHAVIOR FOLLOWING IRRADIATION-INDUCED INJURY IN THE DEVELOPING BRAIN

Akademisk avhandling

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av
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The thesis is based on the following papers or manuscripts:

I. Kalm, M., Fukuda, A., Fukuda, H., Öhrfelt, A., Lannering, B., Björk-Eriksson, T., Blennow, K., Márky, I., Blomgren, K.
Transient inflammation in neurogenic regions after irradiation to the developing brain
Radiation Research, (2009) 171, 66-76.

II. Kalm, M., Lannering, B., Björk-Eriksson, T., Blomgren, K.
Irradiation-induced loss of microglia in the young brain
Journal of Neuroimmunology, (2009) 206, 70-75.

III. Karlsson, N.*, Kalm, M.*, Nilsson, M., Björk-Eriksson, T., Blomgren, K., **Irradiation to the young mouse brain impaired learning and altered the behavior pattern in adulthood and old age**
Manuscript
*these authors contributed equally

IV. Kalm, M., Levin, A., Andreasson, U., Björk-Eriksson, T., Pekny, M., Blennow, K., Pekna, M., Blomgren, K.
C3 deficiency protects against impairment of hippocampal growth and learning induced by irradiation to the young brain
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ABSTRACT

Radiotherapy is used in the treatment of pediatric brain tumors and is often associated with debilitating late effects, such as intellectual impairment. Areas in the brain harboring stem cells are particularly sensitive to irradiation (IR) and loss of these cells may contribute to cognitive deficits. It has been demonstrated that IR-induced inflammation negatively affects neural progenitor differentiation. Therefore, it is necessary to investigate the inflammatory mechanism to be able to find potential treatment strategies. One moderate dose of IR to the young rodent brain caused injuries that were detectable after several months, including impaired growth. We have shown that IR to the developing brain induces an acute inflammatory response. An unexpected finding was that microglia died shortly after treatment. The consequences of IR-induced microglia loss can either be that the injury, due to pronounced inflammation, is decreased, or that injury is enhanced due to weakened repair mechanisms. Further investigations are needed to elucidate how the loss of microglia affects the response to IR and brain development.

The third complement component (C3) is a key protein of the complement system which we found to be upregulated after IR. C3 has been shown to be important for neurogenesis, and therefore we wanted to investigate the role of complement activation after IR by using C3-deficient mice. Interestingly, the IR-induced injury, measured as tissue loss and decrease of proliferating cells, was not as pronounced in the dentate gyrus of *C3*-deficient mice as in wild type mice. This indicates that manipulation of the complement system could be a fruitful strategy to protect the neurogenic areas from IR-induced injuries.

We have studied functional consequences of IR to the growing brain. We saw that one dose of IR to the young rodent brain caused behavioral changes that were detectable months and even one year after the treatment. Furthermore, non-irradiated animals performed better than irradiated ones in different learning tasks. Importantly, months after IR *C3*-deficient mice made fewer errors in place learning and reversal learning tests than WT mice. These results indicate that the complement system contributes to both morphological and functional IR-induced injury in the young brain.

Keywords: radiotherapy, neuroinflammation, microglia, memory, cognition, hippocampus.
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