THE NEUROVASCULAR NICHE AFTER IRRADIATION TO THE DEVELOPING BRAIN

Akademisk avhandling

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av

Martina Boström

Fakultetsopponent:
Professor Amelia J. Eisch
University of Texas Southwestern Medical Center at Dallas

Avhandlingen baseras på följande delarbeten:

I. Irradiation to the young mouse brain caused long-term, progressive depletion of neurogenesis but did not disrupt the neurovascular niche
Boström M, Kalm M, Karlsson N, Hellström Erkenstam N and Blomgren K.
J Cereb Blood Flow Metab 33(6): 935-943 (2013)

II. The hippocampal neurovascular niche during normal development and after irradiation to the juvenile mouse brain
Boström M, Hellström Erkenstam N, Kaluza D, Jakobsson L, Kalm M and Blomgren K.
Submitted

III. Irradiation to the young mouse brain impaired white matter growth more in females than in males
Roughton K, Boström M, Kalm M and Blomgren K.
Cell Death and Disease, In press (2013)

IV. Gene expression in endothelial cells isolated by flow cytometry after irradiation to the young mouse brain
Boström M, Kalm M, Hellström Erkenstam N and Blomgren K.
Manuscript

UNIVERSITY OF GOTHENBURG

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Martina Boström

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

ABSTRACT

Radiotherapy is commonly used in the treatment of pediatric brain tumors but is unfortunately associated with debilitating negative effects, such as impaired memory and learning. Historically, vascular damage following radiotherapy was considered the primary injury which in turn caused ischemia and necrosis. This hypothesis was supported by studies reporting structural changes to blood vessels, such as thickening of the vessel walls, vessel dilation and enlargement of the endothelial cell nucleus. Furthermore, quantitative studies observed time- and dose-dependent loss of endothelial cells, vessel length and density after irradiation. Most experimental studies have, however, focused on the mature brain and used high doses of irradiation. Moreover, the adult brain is capable of generating new neurons throughout life in discrete areas of the brain, and these regions are consistently affected by irradiation. Hence, much research has focused on the neural stem and progenitor cells, since a loss of these cell types has been coupled to cognitive decline after irradiation. Other important cell types have therefore been neglected and need to be examined in order to see the full picture.

In this thesis we investigated the effects after a single moderate dose of cranial irradiation (8 - 10 Gy) to the juvenile brain and focused on the vasculature in different areas. Analysis of vascular structure and complexity up to 1 year after irradiation indicated that the vasculature adjusted to the needs of the surrounding tissue. This was observed in both the hippocampus (gray matter) and the corpus callosum (white matter). We did not observe any apparent endothelial cell death, nor any upregulation of genes involved in endothelial cell death acutely after irradiation. The reduction of neural progenitor cells in the hippocampus was however irreversible and we demonstrated that irradiation in fact accelerated the natural decline in neurogenesis with age. We also investigated the neurovascular niche and found a disruption early after irradiation that however seemed to normalize with time. This hence demonstrated dissociation between the morphological patency of the neurovascular niche and hippocampal neurogenesis.

Using flow cytometry we isolated endothelial cells and investigated gene expression after irradiation. We then surprisingly observed that endothelial cells upregulated proinflammatory genes acutely after irradiation. This has previously not been observed in endothelial cells after *in vivo* irradiation, but indicates that although endothelial cells seem to be less sensitive to radiation, they are involved in the inflammatory response after irradiation.

Keywords: Radiotherapy, hippocampus, neurovascular niche, neurogenesis, microvessels, endothelial cells
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