Molecular events underlying the effect of radiation during neuronal maturation

M. Benotmane[a], J. Verheyde[a], N. Mkarkab[a], A. Michaux[a], A. Janssen[a], M. Neefs[a], S. Baatout[a], L. De Saint-Georges[a] and L. Leyns[b]

[a] *SCK-CEN, Boeretang 200, B-2400 Mol, Belgium;* [b] *Free University of Brussels (VUB), Pleinlaan, 2, B-1050 Brussels, Belgium*

abenotma@sckcen.be

Brain damage induced by prenatal irradiation is of major concern in radioprotection. The brain is the final result of a series of well timed consecutive or concomitant waves of cellular proliferation, migration and differentiation. Acute irradiation during pregnancy could result in various forms of abnormalities such as microcephaly, reduced cortical thickness and mental retardation. Such events were previously described in epidemiological studies of the atomic bomb survivors of Hiroshima/Nagasaki, and from the Chernobyl accident survivors irradiated during embryogenesis (Verheyde and Benotmane 2007). Preliminary data in our laboratory confirmed adult behavioural defects in mice irradiated with low doses (0.2Gy) during the critical period of neurogenesis during gestation (E11, E12). Moreover we showed that radiation induces a reduction in the neurites length in primary neuron cells isolated from the hippocampus, which might interfere with correct patterning of the brain and could jeopardize the formation of a correct neural network, leading possibly to delayed cognitive deficits in the mature adult brain. Using a multilevel molecular approach, we first intend to contribute to the understanding of the mechanisms underlying the effect of radiation during neuronal maturation by: - analysing the profile of gene expression in order to identify genes involved in memory and cognition. - analysing the response of specific inflammatory pathways shown to be involved in radiation damage, or modulated at the transcriptional level from our microarray data.

At the cellular level, we believe that neurite length reduction is a consequence of an inflammatory response rather than a direct consequence of targeted DNA-damage. - the mechanisms of neurite outgrowth after different low doses (0.1, 0.2 Gy) given at different stages of neural maturation. - the modulation of inflammatory responses at the transcriptional and protein levels in vivo, allow to draw a clear picture of the molecular mechanisms contributing to neurite outgrowth and potentially involved in delayed cognitive disorders. The main goal of this study is to shed light on the molecular and proinflammatory cascades induced by an exposure of the mouse developing brain to low doses of ionizing radiation. The responses will help to understand and to correlate delayed adult behavioural deficits as, similar to the results of the epidemiological studies in Hiroshima/Nagasaki and in Chernobyl, since preliminary studies performed in our laboratory have evidenced clear behavioural phenotypes in adult mice that had been irradiated during the critical period of neurogenesis.

This study is supported by The NOTE EC integrated project (FI6R 036465).