FACULTY OF MEDICINE AND HEALTH SCIENCES

INSIGHTS INTO RADIOSENSIVITY AND DEFECTIVE DNA REPAIR IN IMMUNODEFICIENCY SYNDROMES

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SUMMARY

Our DNA is constantly exposed to damage from everyday factors like radiation, environmental toxins, and even during normal cell division. When severe forms of DNA damage, such as DNA double-strand breaks (DSBs), occur, our cells activate specialized repair mechanisms. At the center of these repair systems is the DNA damage response (DDR), a complex network of cellular tools that recognizes and repairs the DNA damage. However, some patients have rare inherited disorders that lead to deficiencies in these repair mechanisms, putting them at risk for severe health problems. These disorders, which often involve the immune system, are known as inborn errors of immunity (IEI) and are frequently associated with an increased cancer risk, developmental abnormalities, and potentially makes patients highly sensitive to ionizing radiation (IR).

Radiosensitivity—the tendency to react severely to IR—poses a unique challenge in these patients. For example, therapies involving radiation, like cancer treatments or hematopoietic stem cell transplants, can cause extreme side effects in radiosensitive individuals. In my doctoral research, we aimed to better identify these radiosensitive patients and further delineate potential genetic causes of radiosensitivity.

To achieve this, the micronucleus (MN) assay was used to assess the level of unrepaired or misrepaired DNA damage following radiation exposure. By studying chromosomal radiosensitivity in fresh blood samples of a large group of genetically and clinically diverse IEI patients, we found that not all DNA DSB repair disorders are characterized by a radiosensitive phenotype. Moreover, the high variability in MN yields observed in the severe radiosensitive patients with ataxia-telangiectasia suggested a correlation between specific genetic variants and the degree of chromosomal radiosensitivity.

Additional MN assay protocols were developed and tested, to make this assay more versatile and accessible in specific research and clinical contexts. This doctoral thesis describes the validation of a fast and simple procedure for the MN assay on cryopreservation of whole blood samples. As an alternative for lymphocyte-based radiosensitivity testing, the MN and γH2AX foci assay were performed on fibroblasts from IEI patients with severe lymphopenia.

The research also involved a patient presenting with a rare genetic condition affecting the *ATRIP* gene, a crucial part of the DDR during replication. Studying this unique case of ATRIP deficiency helped shed light on the broader functioning of the ATRIP protein and revealed previously unknown aspects of its role within the ATR signaling pathway.

The work presented in this thesis highlights the importance of reliable methods for detecting radiosensitivity in patients with DNA repair disorders. The gained insights are essential for improving clinical care and better managing treatment risks for these radiosensitive individuals.

PROMOTORS

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PUBLICATIONS

Beyls E, Baeyens A, Vral A. The cytokinesis-block micronucleus assay for cryopreserved whole blood. International Journal of Radiation Biology. 2021

Duthoo E*, **Beyls E***, Backers L et al. ATRIP deficiency impairs the replication stress response and manifests as microcephalic primordial dwarfism and immunodeficiency. Under revision in Journal of Experimental Medicine.

Beyls E*, Duthoo E*, Backers L, et al. Investigating chromosomal radiosensitivity in inborn errors of immunity: insights from DNA repair disorders and beyond. Under revision in Journal of Clinical Immunology.

Beyls E, De Beul S, Bordon V, et al. Fibroblast-based radiosensitivity assays as a clinically valuable tool for (severe) combined immunodeficiency syndromes. Under review in Mutation Research - Genetic Toxicology and Environmental Mutagenesis.

EXAMINATION COMMITTEE

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ONLINE VERSION PHD THESIS

Available upon request

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