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# Mechanisms of radiation-induced vascular dysfunction

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Endothelial dysfunction is a serious health problem worldwide. One reason for the occurrence of endothelial dysfunction is the process of ageing; although senescent ECs can no longer divide, they are metabolically active and cause significant problems. As they become bigger than other ECs, they disturb the structure of the monolayer; they also become adhesive and secrete inflammatory factors, thereby attracting monocytes that penetrate the EC layer. There is evidence to suggest that other factors can play a part in the development of dysfunctional ECs, such as ionizing radiation. It is this on this aspect that my team is focusing the investigations on. Our research is exploring high acute radiation doses that might be used in radiation therapy for cancer patients, as well as lower doses that accumulate over the course of several years due to occupational and accidental situations, which have affected, for example, nuclear power plant workers and people living near Fukushima. My group has helped introduce a proteomic analysis to the world of radiation biology; proteomics is the large-scale study of the structure and function of proteins. A crucial element of my research is the use of endothelial model systems that are biologically relevant. Cell cultures have proven enormously useful to us, although they are not without their drawbacks; where ECs divide very slowly in the body, they divide approximately every second day in the laboratory conditions. Thus, our team has used ECs isolated from animal models, such as mice, to reflect the real-life situation. Importantly, the use of these models provides us with the possibility to irradiate certain organs and investigate the permanent changes in

the endothelium of that organ. It also enables us to investigate organs that did not receive any irradiation but might be indirectly affected. While endothelial dysfunction brought about through the natural process of ageing cannot be completely halted, the dysfunction brought about through exposure to radiation in daily life, or through procedures such as radiotherapy, is one that can certainly be prevented. Through identifying the precise biological mechanisms of the damage, I hope to pave the way for improvements that could help the ECs to stay intact and reduce incidence of cardiovascular disease around the world.

## Curriculum Vitae

**Education and Career:**

1983 MSc Biochemistry, University of Turku, Finland

1989 PhD Microbiology, Uppsala University, Sweden

1989 – 1991 Postdoctoral fellow, EMBO fellowship, University of Constance, Germany

2003 – 2007 Research Scientist, Federal Office for Radiation Protection, Neuherberg, Germany

2007 – Senior Scientist, Helmholtz Center Munich, Institute of Radiobiology, Neuherberg, Germany, Group Leader Radiation Proteomics

2015 Associate Professor, Medical faculty of Technical University of Munich, Germany

2016 Associate Professor, Proteomics, Faculty of Biochemistry, University of Turku, Finland

**Publications:**

Published 50 full original papers in peer-reviewed journals, 14 reviews, 4 book chapters

**Selected recent publications:**

1. Azimzadeh O, Azizova T, Merl-Pham J, Subramanian V, Bakshi MV, Moseeva M, Zubkova O, Hauck SM, Anastasov N, Atkinson MJ, Tapio S. A dose-dependent perturbation in cardiac energy metabolism is linked to radiation-induced ischemic heart disease in Mayak nuclear workers. Oncotarget. 2016 Jul 6.

2. Bakshi MV, Azimzadeh O, Merl-Pham J, Verreet T, Hauck SM, Benotmane MA, Atkinson MJ, Tapio S. In-Utero low-dose irradiation leads to persistent alterations in the mouse heart proteome. PLoS One. 2016 Jun 8;11(6):e0156952.

3. Sievert W, Trott KR, Azimzadeh O, Tapio S, Zitzelsberger H, Multhoff G. Late proliferating and inflammatory effects on murine microvascular heart and lung endothelial cells after irradiation. Radiother Oncol. 2015 Nov;117(2):376-81.

4. Barjaktarovic Z, Kempf SJ, Sriharshan A, Merl-Pham J, Atkinson MJ, Tapio S. Ionizing radiation induces immediate protein acetylation changes in human cardiac microvascular endothelial cells. J Radiat Res. 2015 Jul;56(4):623-32.

5. Azimzadeh O, Sievert W, Sarioglu H, Merl-Pham J, Yentrapalli R, Bakshi MV, Janik D, Ueffing M, Atkinson MJ, Multhoff G, Tapio S. Integrative proteomics and targeted transcriptomics analyses in cardiac endothelial cells unravel mechanisms of long-term radiation-induced vascular dysfunction. J Proteome Res. 2015 Feb 6;14(2):1203-19.

6. Sievert W, Tapio S, Breuninger S, Gaipl U, Andratschke N, Trott KR, Multhoff G. Adhesion molecule expression and function of primary endothelial cells in benign and malignant tissues correlates with proliferation. PLoS One. 2014 Mar 14;9(3):e91808.

7. Yentrapalli R, Azimzadeh O, Sriharshan A, Malinowsky K, Merl J, Wojcik A, Harms-Ringdahl M, Atkinson MJ, Becker KF, Haghdoost S, Tapio S. The PI3K/Akt/mTOR pathway is implicated in the premature senescence of primary human endothelial cells exposed to chronic radiation. PLoS One. 2013 Aug 1;8(8):e70024.

8. Yentrapalli R, Azimzadeh O, Barjaktarovic Z, Sarioglu H, Wojcik A, Harms-Ringdahl M, Atkinson MJ, Haghdoost S, Tapio S. Quantitative proteomic analysis reveals induction of premature senescence in human umbilical vein endothelial cells exposed to chronic low-dose rate gamma radiation. Proteomics. 2013 Apr;13(7):1096-107.

9. Barjaktarovic Z, Anastasov N, Azimzadeh O, Sriharshan A, Sarioglu H, Ueffing M, Tammio H, Hakanen A, Leszczynski D, Atkinson MJ, Tapio S. Integrative proteomic and microRNA analysis of primary human coronary artery endothelial cells exposed to low-dose gamma radiation. Radiat Environ Biophys. 2013 Mar;52(1):87-98.

10. Sriharshan A, Boldt K, Sarioglu H, Barjaktarovic Z, Azimzadeh O, Hieber L, Zitzelsberger H, Ueffing M, Atkinson MJ, Tapio S. Proteomic analysis by SILAC and 2D-DIGE reveals radiation-induced endothelial response: four key pathways. J Proteomics. 2012 Apr 18;75(8):2319-30.