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Ionizing radiation induces acute and chronic modifications of the transcriptional profile of endothelial cells: A Molecular-functional system biology approach

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Normal tissue damage after radiation therapy is characterised by a chronic altered phenotype of endothelium. Molecular mechanisms involved in the initiation and the acquisition of a chronic activated phenotype of endothelial cells after radiation exposure remain unclear. The aim of this work is to characterize in vitro molecular actors involved in both the acute and late activated phenotype of endothelial cells.

Methods : Human Umbilical Vein Endothelial Cells (HUVEC) were exposed to a single dose of 2 Gy, 20 Gy or a fractionated dose of 10 x 2 Gy. Expression profiling was performed using a Taqman Low density array (TLDA) approach. Gene signature (~500 genes) associated with immune response, apoptosis, angiogenesis, inflammation and protein kinase related genes was performed 0.5, 1, 2, 3, 4, 7, 14 and 21 days after irradiation. Moreover functional assays (Migration and interactions with blood cells) were performed 21 days after irradiation.

Results: Irradiation modifies very rapidly the phenotype of endothelial cells after 2 and 20 Gy. Interestingly 21 days after irradiation, gene expression profile analyses reveal a strong persistent altered molecular profile of HUVECs associated with chronic modifications of functions. Moreover, results showed a specific acute molecular signature at 2 and 20 Gy but also numerous mRNA expression levels modified from 12 hours and remainder modified 3 weeks after 20 Gy. Finally, comparison of the single and the fractionated dose of 20 Gy reveal both specific molecular signatures associated with the total dose and with the regimen of the exposition.

Conclusion : The molecular profile of endothelial cells exposed to ionising radiation is very rapidly modified and kinetic analyses showed that HUVECs acquire a chronic pathological phenotype until 3 weeks after radiation exposure. Our results confirm numerous previous data published in the literature (overexpression of IL-6, IL-8, ICAM1, E-selectin$\cdots$) and reveal modifications, both in acute and chronic response, of the expression levels of numerous molecular actors not described until now as radiation-responsive genes. Our study suggests that our in vitro model is a useful approach to characterise molecular mechanisms involved in the initiation and the acquisition of a radiation–induced chronic pathological phenotype. This model will allow us the molecular modelling of radiation-specific endothelial cell response.

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