Individual susceptibility to radiosensitivity and to genomic instability: its impact on chromatin remodelling and nuclear foci pattern[+]

Adeline GRANZOTTO[1], Clément DEVIC[1], Muriel VIAU[1], Mira MAALOUF[1] and Nicolas FORAY[1*]

[1]*INSERM, U836, Groupe de Radiobiologie, 38042 Grenoble, France ;*

Micro-organisms and rodent models have significantly contributed to the increase of knowledge in the molecular and cellular response to radiation but they have generated specific paradigms far from the clinical reality and have erased the notion of continuum of responses that is daily observed in radiotherapy services (Joubert and Foray, 2006, 2007; Joubert et al. 2008). By gathering a collection of more than 100 human cells representing one of the widest spectrum of radiosensitivity, we pointed out: 1) a quantitative (inverse) correlation between intrinsic radiosensitivity (clonogenic cell survival) and unrepaired DNA double-strand breaks (DSB) recognized by γ-H2AX foci, that is relevant for all the mammalians (Joubert et al. 2008); 2) the existence of a some alternative DNA repair pathway dependent on MRE11 protein that may help in quantifying the radiation-induced genomic instability (Joubert et al. 2008); 3) the importance of the sequestration of active ATM forms in cytoplasm (Pereira et al., submitted). Based on the quantitative DSB repair data obtained from this systematic study, the definition of 3 groups of radiosensitivity was proposed (Joubert et al. 2008). Interestingly, cells from patients showing moderate radiosensitivity and high genomic instability show also spontaneous DNA single-strand breaks likely due to the uncontrolled MRE11 nuclease activity. As a consequence, the pattern of the γ-H2AX foci is completely different from that observed in cells from radioresistant patients: they are more numerous and very tiny. We have proposed a model called the *Christmas lights* that explains such a difference of pattern and may be useful to understand the quantitative link between chromatin remodelling, foci pattern, individual susceptibility and specific irradiation protocols.

References

Joubert A and Foray N. Repair of radiation-induced DNA double-strand breaks in human cells: history, progress and controversies (Chapter 10). In: Landseer, BR, ed. New Research on DNA Repair. Hauppauge NY: Nova Science Publishers, Inc ; 2006.

Joubert A and Foray N. [Intrinsic radiosensitivity and DNA double-strand breaks in human cells]. Cancer Radiother 11:129-142; 2007.

Joubert A, Zimmerman K, Bencokova Z, Gastaldo J, Rénier W, Chavaudra N, Favaudon V, Arlett CF, and Foray N. DNA double-strand break repair in syndromes associated with acute radiation response: a balance between DNA-PK- and MRE11-dependent pathways. International Journal of Radiation Biology. Int J Radiat Biol 84:107-125; 2008.