Investigating the role of defective DNA repair mechanisms in hematopoietic aging

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The ERCC1-XPF heterodimer is an essential component of DNA repair pathways such as nucleotide excision repair (NER) and DNA interstrand crosslink (ICL) repair. Whereas Ercc1 -/- knockout mice develop normally, they quickly develop severe wasting that culminates in death in their fourth week of life due to accelerated progeria[1]. By contrast, XPF knockout mice present with a much milder phenotype. Interestingly, Ercc1 -/- mice harbour hematopoietic defects which are consistent with premature aging[2]. Specifically, in Ercc1 -/- mice hematopoietic progenitors are severely depleted as a result of increased senescence, leading to a decrease in hematopoietic proliferative reserve capacity. In addition, a severe underlying erythropoietic deficit was evident in Ercc1 -/- mice as (i) fetal liver erythropoiesis was markedly reduced, (ii) erythroid progenitors were the most severely depleted of all other lineage progenitors in colony forming assays and (iii) stress erythropoiesis was significantly impaired[2]. Besides its role in DNA repair, the ERCC1-XPF heterodimer has also been shown to fulfil important gene regulatory functions in transcription initiation and epigenetic remodelling of the promoters of developmentally regulated genes, including imprinted genes, by interactions with the basal transcription initiation machinery and with CTCF and the cohesin complex[3,4]. The objective of this project is to use the Ercc -/- mouse progeria model to obtain molecular and cellular insight as to the involvement of DNA repair pathways in hematopoietic aging, with a focus on erythropoiesis. This will entail:
(i) investigating the lineage commitment and differentiation potential of DNA repair-defective aged hematopoietic stem cells (HSCs) from Ercc1 -/- mice
(ii) establishing the transcriptomic profiles, transcription factor occupancies and epigenomic landscapes of HSCs, of select hematopoietic progenitors and of the erythroid lineage in wild type and in the Ercc1 -/- mouse progeria model
(iii) establishing the genome wide occupancies of Ercc1 and XPF in HSCs and in the erythroid lineage in wild type mice and in Ercc1 -/- and Xpf -/- mouse models.
(iv) investigating the XPF protein interactome in erythropoiesis in wild type mice[4] *vs.* the Ercc1 -/- progeria model
The ESR will carry out secondments in (i) UMGC to obtain training in HSC isolation, colony assays and profiling or transcriptomes and epigenomes by NGS (Next Generation Sequencing) and (ii) FORTH in training to use the mouse models of progeria.
The ESR will be enrolled in the PhD Program in Translational and Molecular Medicine - DIMET at the University of Milano-Bicocca http://www.dimet.org/

1. Weeda et al., Current Biology 7:427-439 (1997)
2. Prasher et al., EMBO J 24:861-871 (2005)
3. Kamileri et al., PNAS 8:2995-3000 (2012)
4. Chatzinikolaou et al., Nature Cell Biol. 19:421-432