LABORATORY OF CANCER GENOMICS AND AGING
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BACKGROUND

Protection from cancer and ensured longevity are tightly linked in mammals. Cancer and aging both increase as a function of time and both processes are linked to an accumulation of macromolecular damage. Interestingly, a number of syndromes with congenital DNA repair defects suggest that impaired genome maintenance accelerates aging and contributes to cancer. Distinct types of lesions distort the helix, pause or obstruct DNA replication, block ongoing transcription or else hamper the battery of repair systems and other caretakers that continuously safeguard the genome. The detrimental and adverse short- and long-term effects of DNA damage on the overall organismal survival have forced cells to evolve intricate defense mechanisms that continuously scan, detect and repair DNA injuries inflicted in their genome.

Nucleotide excision repair (NER) is a major repair mechanism that mammalian cells employ to restore their damaged DNA back to its original form. NER is divided into two subpathways: transcription-coupled NER (TCR) that focuses on the transcribed strand of active genes and global genome NER (GGR) that scans for DNA lesions on the entire genome. Evidence in mice and humans suggests a division of tasks amongst these two distinct repair modes: congenital defects in TCR lead to premature aging syndromes but show no cancer predisposition. In contrast, defects in GGR often show a >2,000-fold risk to develop skin cancer but no signs of progeria.

Thus, certain DNA repair defects that give rise to progeroid syndromes likely activate tumour suppressor pathways. Instead, others fail to trigger mechanisms that protect against cancer allowing tumours to persist.

RESEARCH

This is a newly founded lab at the IMBB Institute. Its long-term goal is to delineate the role of DNA damage in cancer and aging. To this end, we will use genetically modified mouse models that mimic human progeroid and cancer predisposition syndromes.

1. The impact of progeroid mutations on tumour development

This project aims at investigating the individual impact of progeroid Csbm/m and XpdTTD mutations in a well-characterized in vivo tumour model for intestinal neoplasias (i.e. the ApcMin/Apc+ mouse tumour model). The novelty of this approach is the combination of a unique set of DNA repair-deficient mice (Csbm/m and XpdTTD) that exhibit dramatically accelerated aging phenotypes with mice that show tumour predisposition (ApcMin/Apc+). Initially, we will investigate whether the progeroid Csbm/m and XpdTTD mutations can substantially decrease the tumour burden and yield a long-term survival benefit for ApcMin/Apc+ mice. In parallel, we will utilize advanced genomics, cell biological and biochemical approaches to identify genes and pathways that are crucial in early, intermediate and advanced stages of carcinogenesis, providing us both with mechanistic insight into this complex process as well as gene targets for its experimental modulation in the future.

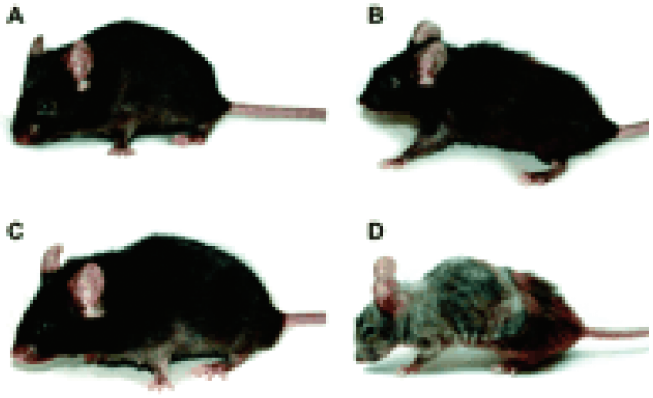

Figure. 1. *XpdTTD mice develop normally and then show a premature aging phenotype. Shown are wt* (*A and C*) *and XpdTTD* (*B and D*) *mice at age ~3 months* (*A*) *and* (*B*) *and 15 to 16 months* (*C*) *and* (*D*). *Progeroid symptoms* (*cachexia and kyphosis*) *start to develop in XpdTTD mice at age 3 to 4 months onward and become increasingly severe.*

2. The impact of impaired transcription on aging and age-related pathologies

The accumulation of unrepairable DNA lesions in the genome hampers the process of transcription by blocking RNA synthesis potentially preventing the generation of messenger RNA and the encoded protein of a gene. Even more, as DNA lesions interfere with gene expression, they also affect a number of vital responses critical for the survival of a cell against hazardous threats. In collaboration with Dr. I. Talianidis lab, we have recently identified substantial genome-wide expression similarities between a number of TCR-defective, progeroid mice and mice that carry defects in transcription factor IID (TFIID) complex. Thus, we aim to further investigate the role of impaired transcription in aging by employing mouse models that carry defects in transcription initiation or elongation. Initially, we will focus on a tissue-specific knockout mouse model carrying defects in the TAF10 subunit of the TFIID complex. By using a number of advanced molecular, genomics and imaging approaches as well as a number of DNA repair-related assays; we will investigate the role of compromised transcription in genome maintenance, progeria and age-related pathology. Finally, as anticancer drugs (i.e. ET-743 and illudin S) specifically interact with TCR and transcription, we also aim to explore the role of transcription as a potential tumour therapy target.

Representative publications

1. van der Pluijm I*, Garinis GA*, Brandt RM, Gorgels TG, Wijnhoven SW, Diderich KE, de Wit J, Mitchell JR, van Oostrom C, Beems R, Niedernhofer LJ, Velasco S, Friedberg EC, Tanaka K, van Steeg H, Hoeijmakers JH, van der Horst GT: Impaired genome maintenance suppresses the growth hormone--insulin-like growth factor 1 axis in mice with Cockayne syndrome. PLoS Biol 2007, 5:e2 (*equal contribution).

2. Niedernhofer LJ, Garinis GA, Raams A, Lalai AS, Robinson AR, Appeldoorn E, Odijk H, Oostendorp R, Ahmad A, van Leeuwen W, Theil AF, Vermeulen W, van der Horst GT, Meinecke P, Kleijer WJ, Vijg J, Jaspers NG, Hoeijmakers JH: A new progeroid syndrome reveals that genotoxic stress suppresses the somatotroph axis. Nature 2006, 444:1038-1043.

3. Jans J*, Garinis GA*, Schul W, van Oudenaren A, Moorhouse M, Smid M, Sert YG, van der Velde A, Rijksen Y, de Gruijl FR, van der Spek PJ, Yasui A, Hoeijmakers JH, Leenen PJ, van

der Horst GT: Differential role of basal keratinocytes in UV-induced immunosuppression and skin cancer. Mol Cell Biol 2006, 26:8515-8526 *equal contribution.

4. Garinis GA, Mitchell JR, Moorhouse MJ, Hanada K, de Waard H, Vandeputte D, Jans J, Brand K, Smid M, van der Spek PJ, Hoeijmakers JH, Kanaar R, van der Horst GT: Transcriptome analysis reveals cyclobutane pyrimidine dimers as a major source of UV-induced DNA breaks. EMBO J 2005, 24:3952-3962

GROUP MEMBERS

To be appointed soon.

COLLABORATORS

1. Dr. Jan H. Hoeijmakers, Erasmus University, Rotterdam, the Netherlands.
2. Dr. Iannis Talianidis, Alexander Fleming Institute, Greece
3. Dr. Andy Bartke, University of Illinois, USA

FUNDING

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