32 Mechanisms of Ageing and Longevity

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Aging, long thought to be solely the byproduct of wear and tear, is actually a highly controlled process, regulated by a combination of genetic and environmental factors. Our overarching goals are: (1) to understand the molecular mechanisms by which known 'longevity genes' regulate aging in mammals; and (2) to discover novel genes and processes that control lifespan using two genetic models for aging: the nematode *C. elegans* and the extremely short-lived African fish *N. furzeri*. We are particularly interested in the aging of the nervous system. My presentation will be focused on the importance of stem cells in the brain during aging in mammals. In the nervous system, neural stem cells (NSCs) are thought to be important for learning, memory, and mood regulation. During aging, both the pool of NSCs and their ability to give rise to new neurons decline, raising the possibility that NSC depletion may underlie part of the cognitive dysfunctions during aging. However, the molecular mechanisms that regulate the maintenance of the NSC pool throughout lifespan are largely unknown. We have found that FoxO3, a member of a transcription factor family known to extend lifespan in invertebrates, maintains the NSC pool in adult mice. Analysis of the program of genes regulated by FoxO3 in NSCs suggests that FoxO3 maintains the adult NSC pool by inducing a program of genes that preserves cellular quiescence and regulates oxygen metabolism. Because NSCs are thought to be important for cognitive function and mood regulation, the ability of FoxO3 to maintain the NSC pool in adult organisms might have important implications for counteracting brain aging in long-lived species, including humans.

33 Proffered Paper: Age-associated Cytokine Signaling Impairs Epidermal Stem Cell Function

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Introduction: Two processes that are intrinsically linked to tumor initiation are the age of the tissue where the tumor develops, and the deregulation of tissue-specific stem cell proliferation. However, how aging specifically alters stem cell function in such a way that may facilitate tumor development is not clear. This highlights the necessity to understand how stem cells respond to, and are altered by the normal aging process in order to better understand tumor initiation and progression.
Materials and Methods: We phenotypically and molecularly characterized epidermal stem cell aging in mice at different stages throughout the normal lifespan. We FACS sorted a highly purified population of aging stem cells and performed high-throughput RNA-sequencing analysis on these cells to uncover novel age-associated changes, which we then functionally validated using *in vitro* and *in vivo* stem cell assays.
Results and Discussion: Surprisingly, we discovered that during the aging process, the Keratin-15 positive population of epidermal stem cells displays previously unseen age-associated changes, including increasing significantly in number, while decreasing in functional capacity, both normally and in response to damage. Using high-throughput RNA-sequencing of purified aging stem cells, coupled with cytokine arrays on aging tissues, we identified aberrant cytokine signaling derived from the epidermis as a major alteration that occurs during the normal aging process. Furthermore, we demonstrate that these inflammatory signals can impact epidermal stem cell function and likely contribute to the age-mediated decline seen in the tissue. Importantly, we found that chemical inhibition of Jak/Stat signaling, a critical mediator of cytokine signaling, reverses the age-mediated decline in stem cell function and restores aged stem cell capacity both *in vitro* and *in vivo* in the adult skin.
Conclusion: Enhanced tumor suppression is suggested as playing a causative role in the aging process. Our data uncovers chronic cytokine signaling during aging as an inhibitor of normal stem cell function, possibly as part of a broader tumor suppressive response. However, a consequence of this is the accumulation of a population of altered stem cells that are frequently targeted during tumor initiation that may prime aged tissue for tumor development. Ultimately however, the net effect is the inhibition of stem cell function, which likely contributes significantly to the aging process.

34 Ageing and Cancer: the Somatotropic Link

No abstract received.

Sunday 8 July 2012 12:15–13:00

EMBO Lecture: Cancer Genomics

35 The Genomics of Drug Sensitivity in Cancer

M. Stratton[1], M. Garnett[1], E.J. Edelman[2], S. Heidorn[1], P.A. Futreal[1], D. Haber[2], S. Ramaswamy[2], U. McDermott[1], C. Benes[2]. [1]*Wellcome Trust Sanger Institute, Cancer Genome Project, Cambridge, United Kingdom,* [2]*Massachusetts General Hospital Cancer Center, Harvard Medical School, Charlestown, USA*

Clinical responses to anticancer therapies are often restricted to a subset of patients. In some cases, for example the presence of the *BCR-ABL* translocation or point mutations in *BRAF*, mutated cancer genes are potent biomarkers of response to targeted agents. To uncover new biomarkers of sensitivity and resistance to cancer therapeutics, we are systematically screening a panel of several hundred cancer cell lines, which represent much of the tissue-type and genetic diversity of human cancers, with hundreds of drugs in clinical use or under preclinical investigation. We have found that mutated cancer genes are associated with cellular response to most currently available cancer drugs. Classic oncogene addiction paradigms are modified by tissue-specific or expression biomarkers, and some frequently mutated genes are associated with sensitivity to a broad range of therapeutic agents. Unexpected relationships have been revealed, including the marked sensitivity of Ewing's sarcoma cells harboring the *EWS-FLI1* gene translocation to PARP inhibitors. By linking drug activity to the functional complexity of cancer genomes, systematic pharmacogenomic profiling in cancer cell lines provides a powerful biomarker discovery platform which can guide rational cancer therapeutic strategies and trial design in the future.

Sunday 8 July 2012 14:30–15:15

OECI Lecture: Cancer Systems Biology

36 Network and Systems Biology in Cancer

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Biological systems integrate metabolic, energy and signaling networks, by maintaining dense webs of control circuits and multiple adaptors common to two or more interfacing networks. My lecture will concentrate on systemic defects in signaling networks involved in malignant cell proliferation and migration. As a starting point, I will argue that primordial signaling pathways have been replaced in the course of metazoan evolution by layered signaling networks. The driving process behind this transformation has been whole genome duplications, which established modularity, an essential feature of biological robustness. Other features of robustness include redundancy and systems control, primarily feedback and feed-forward loops that maintain homeostasis and determine the outcome of network activation.
Unlike linear pathways, networks can be trained to overcome perturbations, and their control wirings are much more sophisticated. These transitions are relevant to pharmacological attempts to intercept signaling networks, as well as to the excessive reliance of oncogenic networks on 1–2 essential hubs ('oncogene addiction'). Using the epidermal growth factor receptor (EGFR) and its kin, a kinase called HER2/ERBB2, I will exemplify defects in system control and feedback regulation, and highlight some of the currently approved drugs that target the EGFR-HER2 axis. Along with illuminating the rationale of combination therapies, the lecture will focus on acquired (secondary) resistance to molecular targeted therapies, as an exemple of the remarkable adaptation capacity of signaling networks.

Sunday 8 July 2012 15:15–16:00

Award Lecture: Anthony Dipple Carcinogenesis Award

37 Causes and Consequences of microRNA Dysregulation in Cancer

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Since the discovery of miR-15a and miR-16-1 deletions in CLL15, many laboratories around the world have shown miRNA dysregulation in all tumours studied, including the most common, such as lung, breast, prostate and gastrointestinal cancers. Such dysregulation, like the dysregulation of oncogenes and tumour suppressor genes, can be caused by multiple mechanisms, such as deletion, amplification, mutation, transcriptional dysregulation and epigenetic changes.