ONGOING RESEARCH AND RESEARCH-RELATED PROJECTS

A. Basic Research on Cancer and Aging (*Biology of Aging Laboratory*)

A. Feki, MD-PhD student; C.E. Jefford, PhD student; A. Caillon, technician; M. Hardy, diploma student, Fabrice Callabrio, diploma student

The function of cancer susceptibility genes and the molecular pathways in which they are involved are the focus of our studies. In particular we are working on BARD1, a protein associated with the product of the breast cancer gene BRCA1. We have recently demonstrated that BARD1 is upregulated upon cellular stress and induces apoptosis in a BRCA1-independent way. BARD1 seems to explicitly implement its apoptotic function during morphogenesis, in response to "damage", and in maintaining tissue homoeostasis. Corroboration of each of these functions could explain tumorigenesis. A reduction of BARD1-specific apoptosis is suspected during the aging process and could provide one explanation for increased cancer risk with age.

Studies on BARD1 expression, structure and function

One branch of our projects is aimed at the elucidation of molecular mechanisms that are implicated in BARD1 functions. We are interested in identification of the factors that are involved in the transcriptional regulation of BARD1 expression under various conditions and the respective BARD1 promoter elements. Secondly, we are interested in characterizing the structure-function relationship of the BARD1 protein, by generating GFP-tagged BARD1 deletion mutants and studying their respective intra cellular location and co-localization with a number of other proteins (BRCA1, p53, mdm2, PCNA, etc.), as well as their apoptotic capacity. Third, we are searching for the protein interaction partners of BARD1 and BARD1 deletion or point mutants. In particular we are interested in the characterization of the mechanism of p53 stabilization by BARD1.

Role of BARD1 in tissue homeostasis

To demonstrate the relevance of the apoptotic function of BARD1 in vivo, we are studying BARD1 expression under physiological and pathological conditions in a variety of organs. We have recently published that BARD1 expression is upregulated after ischemia in the brain where normally no BARD1 expression can be detected. We have now expended this research on other organs, such as heart, muscle, lung, ovary, breast, spleen, and testis. As determined by immuno-histochemistry, BARD1 expression coincides with apoptotic events. Ongoing projects involve the specific role of BARD1 under physiological and pathological conditions. For example, little BARD1 expression is found in normal lung tissue, but dramatically elevated levels in fibrotic tissue. We will determine whether the mechanism of BARD1 induction is dictated by each particular organ, or depends on the specific stress that leads to the pathology. The research on the role of BARD1 in spermatogenesis has produced most significant advancements, leading to identification of BARD1 activation factors, cloning of testis specific isoforms, and the characterization of BARD1 apoptotic function to normal spermatogenesis and human pathologies.

BARD1 in tumorigenesis

We have previously reported that antibodies against an apoptotic cleavage product of BARD1 were discovered in rats immunized against tumor development. This finding is consistent with a function of BARD1 in early tumorigenesis. To sustain this view BARD1 expression is studied in samples of staged ovarian and breast tumors.

BARD1 function studied in animal models

We are study of BARD1 function in tumorigenesis in an animal ovarian cancer model. The ovarian cancer cell line Nutu-19 induces ovarian tumors and metastases when injected intraperetonially into rats. NuTu-19 cells are deficient of a functional BARD1 gene and resistant to apoptosis by DNA damage inducing agents. a and projects towards an application of BARD1 in cancer therapy.

During the aging process the function of repair genes seems to be diminished and might explain the increased cancer risk with age, which is currently investigated in clinical studies (Collaboration Dr. G. Zulian, Geneva).

Novel Markers of Aging and Aging-Associated Diseases (*Monitoring Laboratory*)

C. Genet, L. Ortolan-Trigui, F. Piotton, technicians, Stephan Ryser, postdoc

We have established a test for the prediction AD based on the detection of Tau and Ab-42 in the cerebrospinal fluid and demonstrated that Tau protein levels increase as a function of age and that different kinetics of increased are observed in women and men, while the concentrations of Ab-42 are not increasing with age in normal individuals but are higher in men than in women. (Collaborations with: Dr. P. Burkhard, Geneva; Prof. S. Bourras, Geneva)

A second test we have established is based on the phenomenon of telomere shortening in somatic cells. We are interested to determine telomere length in different tissues and to demonstrate a decrease of telomeric sequences in response to oxidative stress and independent of chronological age. Using animal models to characterize the relationship between oxidative stress and telomere shortening, we have observed a striking correlation in lymphocytes. We are now in progress to develop these methods further to determine i) telomere length in other tissues and ii) telomere length and telomerase activity in tumors and pre-malignant tissues as predictive markers.

Newly started projects: Geneva cohort studies on longevity and cancer predisposition.

Towards the creation of an Aging Research Center Geneva "ARC Geneva"

The medicine of the old age and the biomedical research in this domain is of increasing importance in modern medicine. Taking into account the strong Geneva tradition in clinical care of the elderly and in research on aging, we suggest to unify the forces working on the subject in a research center on aging. This new concept implies to gather in one place the different research groups in the aging field, from the psychosocial to the molecular type of research, with the aim of a global understanding of the phenomenon of aging and its handling by our society.

ARC-Geneva

Aging research differently: interactive, synergistic, expandable, transformable...transparent.

See: I. Irminger-Finger, et al., (2001). Pour la création d'un centre de recherche sur le vieillissement à Genève. Médecine & Hygiène 2368, 2255-2256.

Towards the creation of a PhD- MD program at the faculty of medicine, University of Geneva

Several arguments can be produced in favor of a new educational program designed for PhDs working in medical science. First, today's progress in science is advancing most rapidly in the field of medical science. This implies an increased need for scientist in this field, which is today covered by strongly motivating medical students to choose a scientific career. Secondly, MDs, by their actual education are not trained to do high quality research and cannot catch up easily on what is learned in a regular PhD program. PhDs do obviously not have the medical background. Third, a synergy of both seems obvious. Today's research is done in networks, thus integrating the expertise from different fields. However, the outcome of interactive research strongly depends on the ability to communicate and mutual comprehension. The presumed novel PhD-MD program will generate scientists who understand and know basic medicine and will be able to communicate with "normal" doctors. This strategy will be necessary for a future successful biomedical science, to avoid loss of intuitive knowledge from the health professional, "because there was nobody who understood", and it will avoid the "reinventing the wheel"

by clinicians who do not know enough basic biology.