Selected Orals

O1

Innate immunity of blood leukocytes of senile diseases patients

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Background: As deficiency of innate immunity was found by us earlier in elderly (> 60) and also in leukemia patients, the innate immunity of blood leukocytes obtained from tumorous patients (carcinoma ovarii and adenocarcinoma endometrium), Alzheimer disease (AD) patients and control group in the same age was compared. Two of the mechanisms engaged in innate immunity were studied:
— resistance of leukocytes ex vivo to viral infection,
— production of cytokines (TNFα, IFNs, IL-10, IL-12)

Methods: The resistance of leukocytes was designated just after isolation by infection with vesicular stomatitis virus (VSV). Titer of VSV 0-1 log TCID50 indicate for complete resistance, titer 2–3 log for partial resistance, > 4 log indicate for very low or lack of resistance. Cytokines were assayed with ELISA test.

Results: Results of experiments showed that leukocytes of the three groups are very sensitive to VSV infection. In contrary, the basic differences in cytokines production by leukocytes of these groups. The leukocytes of cancer group (n = 15) produced more TNFα than control (n = 10) and AD group (n = 35), less IFNs and IL-10, and not et all IL-12. The leukocytes of AD patients produce high level of early IL-12 and IL-10 (spontaneous and VSV-induced) and less than control TNFα and IFNs.

Conclusion: The sensitivity of leukocytes to VSV in these three groups is caused by deficiency of innate antiviral immunity. Different panel of cytokines produced by leukocytes of patients with senile diseases may participate in their development: TNFα in cancer and IL12 in AD.

O2

Aging, longevity, and cancer: common gene signature

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Background: Several lines of evidence suggest strong association between aging/longevity and cancer: (i) the prevalence of cancer incidences in advanced age, (ii) the high rate of cancer in premature aging, and (iii) the delay of or escape from cancer in animal models of life span extension and in humans of exceptional longevity. This implies the existence of common molecular basis for aging/longevity and cancer. If so, the genes affecting aging/longevity could also be involved in cancer and vice versa. We have recently constructed a Human Longevity Network (HLN) based on protein-protein interactions (PPIs) between established longevity-associated proteins and their first-order interacting partners (Budovsky et al., 2007, Mech Ageing Dev 128: 117–124). Similarly, Human Cancer Network (HCN) was constructed based on PPIs of cancer-associated genes. Both networks are characterized by the presence of highly connected nodes (hubs) and display a scale-free topology. The comparison between HLN and HCN showed that they share a significant overlap. Over 85% of the HLN nodes and 90% hubs are present in HCN. Considerable portion of the common nodes and especially hubs are involved in other human age-related diseases (ARDs) as well. These genes are highly evolutionary conserved and fall into three main categories: signal transduction, DNA maintenance and repair, and protein and energy metabolism. Many of the common genes are under epigenetic control which patterns are similar in both aging and cancer. This includes a global hypomethylation accompanied by activation of the oncogenes, and gene-specific hypermethylation which affects preferentially the tumor suppressors. Furthermore, some of the common genes undergo age-related changes in their expression (most likely because of epigenetic modifications) as revealed by the analysis of DNA microarray data reported for humans of different age. Collectively, the results obtained support our hypothesis that aging should be considered a major risk factor for life-threatening degenerative pathologies including cancer and suggest that common mechanisms stand behind both aging and ARDs (Budovsky et al., 2006, Rejuvenation Res 9: 207–210). The network-based approach could be useful for searching the common drug targets for curing the ARDs and promoting longevity.
Involvement of oxidative DNA damage and antioxidant status in human aging

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Aging is a complex process involving morphologic and biochemical changes in single cells and in the whole organism. One of the most popular explanations of how aging occurs at the molecular level is the oxidative stress hypothesis. The aim of this work was to assess age-related changes in oxidative DNA damage in 255 humans, 3–83 years old. For the first time, the broad spectrum of oxidative DNA damage biomarkers was analysed; urinary excretion of 8-oxodG and 8-oxoGua as well as the level of oxidative DNA damage in leukocytes. In addition a concentration of antioxidants vitamins A, C, E and uric acid was determined in blood serum. The level of 8-oxodG in leukocytes’ DNA showed statistically significant correlation with age of examined subjects, and the level of urinary 8-oxoGua and 8-oxodG followed the same pattern. Age-dependent decline in the concentration of vitamin C, small but statistically significant increase in the level of vitamin E and gradual increase of uric acid with age was observed. On the basis of presented correlative association between oxidative DNA damage parameters and age it seems reasonable to state that the damage may be one of the substantial factors of human aging. Furthermore, inverse correlation of vitamin C concentrations with age is also consistent with the oxidative stress hypothesis of aging.

Mass spectrometry tools for characterising oxidatively damaged proteins

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Oxidative stress mediated modifications of proteins proceeds according to a variety of mechanisms some of which lead to backbone peptide cleavage, amino acid side chains modifications and protein aggregation. Oxidative modification of amino acids side chains includes the introduction of carbonyl groups, by direct oxidation or via conjugation reaction to reactive secondary oxidation products that arise, from for example, lipid peroxidation or advanced glycation end products. Carbonylated proteins/peptides have been a major target for quantification of oxidized proteins based on DNPH (2,4-dinitrophenylhydrazine) derivatisation followed by UV spectroscopy or immunochemical detection using anti-DNPH primary antibody. However these methods are limited by the fact that they do not readily allow identification of the nature of the modification and quantification of oxidation sites in proteins, which is of critical importance in the study of disease associated protein oxidation. Here we present mass spectrometry-based approaches that are at least in part capable of overcoming some of these limitations.
**O5**

**Activation of anti-proliferative cell fate programs in several cell types of TPPII deficient mice**

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The giant cytosolic protease tripeptidyl peptidase II (TPPII) has been implicated in the regulation of proliferation and survival of malignant cells, particularly lymphoma cells. To address its functions in normal cellular and organismic physiology we have generated TPPII-deficient mice. TPPII deficiency affects the proliferative capacity of several cell types including T lymphoid cells and fibroblasts, impairing proliferative survival by promoting apoptosis of the former and inducing premature cellular senescence of the latter. These alterations coincide with upregulation of p53 and deregulation of NF-κB. Lack of TPPII causes degenerative alterations at organismic level, as suggested by a decreased life span and symptoms characteristic of premature hematopoietic senescence. These include accelerated thymic involution, reduction in peripheral T lymphocytes, impaired proliferative T cell responses, extramedullary hematopoiesis and inflammation. These results suggest that TPPII is important in maintaining normal cell physiology at organismic level, which may be relevant for potential therapeutic applications of TPPII inhibitors.

**O6**

**D-glucarates as mimetics of calorie restriction and proapoptotic agents**

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Although calorie restriction (CR) remains the most robust intervention for slowing aging and maintaining health and vitality, CR mimetics could also provide a practical anti-aging strategy. Since CR was found to reduce circulatory levels of the enzyme β-glucuronidase we propose to study naturally occurring β-glucuronidase inhibitors, D-glucarates, as CR mimetics. While β-glucuronidase is important to maintain healthy life, its overexpression may facilitate the development of cancer. Our overall hypothesis is that D-glucarates, by causing a moderate inhibition of β-glucuronidase may increase life span of mice and, possibly, humans. The accumulation in the body of free carcinogens, tumor promoters and other toxins, normally excreted as glucuronides in the bile or urine, may be aggravated not only by the elevated β-glucuronidase activity but also by the depressed synthesis of the β-glucuronidase inhibitor D-glucaro-1,4-lactone. There is now growing evidence from short- and long-term models, for the possible control of different stages of the carcinogenic process by D-glucaro-1,4-lactone, and specifically by its precursors such as D-glucaric acid salts (D-glucarates). Our recent studies indicate that D-glucaro-1,4-lactone and D-glucarate have antiproliferative properties as well as anti-inflammatory properties similar to those of calorie restriction. The present study provides evidence on the ability of calcium D-glucarate (CG) to inhibit target cell proliferation (i.e., cells with mutated K-ras) and inflammation and to induce apoptosis during post-initiation stages of benzo[a]pyrene B[a]P-induced lung tumorigenesis in A/J mice. Thus, 2% and 4% CG diets reduced significantly the number of lung adenomas 4 months after B[a]P gavaging and increased, in a dose related fashion, levels of caspase 3 and 9 as well as cleaved PARP in the lung tissue. At the same time, a marked inhibition of cyclooxygenase 2 (COX-2) was detected. We conclude that post-initiation D-glucarate may inhibit B[a]P-induced tumorigenesis in A/J mice by suppressing cell proliferation and chronic inflammation and by increasing programmed cell death. We predict that chronic treatment of mice with D-glucarates may not only prevent cancer but it may also extend healthy life span in a manner similar to calorie restriction.
Senescent human peritoneal mesothelial cells may stimulate ovarian cancer progression through a VEGF-dependent mechanism

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We have previously described the mechanisms underlying senescence of human peritoneal mesothelial cells (HPMC) in vitro. Because the peritoneal cavity is the prime site for the ovarian cancer to metastasize, we have set out to examine whether senescent HPMC display properties that may promote the intraperitoneal invasiveness of ovarian cancer cells.

The experiments were conducted using ovarian cancer cell line OVCAR-3 and omentum-derived HPMC. Conditioned media (CM) were collected from early-passage and senescent HPMC over the period of 3 days under serum-free conditions. OVCAR-3 proliferation was measured by 3H-thymidine labelling. VEGF concentrations were assessed with ELISA, and the activation of the transcription factors HIF-1 and NF-xB was assessed using the Trans-AM assays. The data were expressed as means ± SEM, and analyzed with the paired t-test.

VEGF secretion by senescent HPMC was (pg/10^5 cells) 709±71 compared to 326±66 for early-passage cells (P<0.0001, n=31). This effect was accompanied by increased activation of the transcription factors known to regulate the VEGF gene. Nuclear expression of HIF-1 and NF-xB (p65) in senescent cells was, respectively, 127% and 215% of the levels seen in early-passage cells. OVCAR-3 proliferation in the presence of CM from senescent HPMC was significantly increased compared to CM from early-passage cells (10404±37497 vs 22647±5334 cpm/10^5 HPMC, n=9, P<0.0001). The addition of anti-VEGF neutralizing antibody to HPMC-derived CM resulted in a 50±12% reduction in OVCAR-3 proliferation (P<0.04, n=4). In contrast, exposure to recombinant human VEGF resulted in a dose-dependent increase in OVCAR-3 cell growth. VEGF at dose comparable to that found in CM (1 ng/ml) stimulated OVCAR-3 proliferation by 18±10%. These results indicate that senescent HPMC display a phenotype that favours VEGF release. Furthermore, HPMC-derived VEGF may directly promote ovarian cancer cell growth, independently of its angiogenic properties.

Decline of T cell related immune functions in cancer patients and a trial of immunological restoration by infusion of activated T cells

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The immune system plays an important role in the suppression, growth and metastasis of cancer, such that its increased incidence with age may be related to an age-related decline of immunity. However, the assessment of immune function is complex. To this end, we developed a system measuring different immune markers and functions according to a data base of known age-associated immune changes. Using this scoring system, we combine many different immunological parameters for individuals, which can be expressed as a simple numeric indicating immune status. We examined 103 patients with colorectal cancer and 51 healthy age-matched controls using this immunological scoring system. All patients underwent surgical resection and their tumors were assessed by pathology to determine their stage according to the WHO criteria. Some cases were treated with chemotherapy and its effect on immune functions was also examined. Blood samples were obtained 1 day before surgery, and 1 week and 1 month thereafter, and subjected to the immunological analyses. Parameters examined included the numbers of T cells, CD4+ cells, CD8+ cells, naïve T cells, memory T cells, CD4+CD25+ regulatory T cells, B cells and CD16+CD56+ NK cells, as well as proliferative activity of T cells. The ratios of CD4+ T cells/CD8+ T cells and of naïve T cells/memory T cells were calculated. The T cell immune score is a summation of scores of 3 T cell-related parameters; number of T cells, number of naïve T cells, ratio of CD4+ T cells/CD8+ T cells, ratio of naïve T cells/memory T cells and proliferative activity of T cells. Restoration to normal immune status was attempted in cancer patients by infusion of activated T cells which were prepared by culturing autologous lymphocytes with immobilized anti-CD3 antibody and IL-2 for 7 to 10 days. Results obtained were 1) The T cell immune score showed a gradual decline with age in healthy people; this age-related decline was more prominent in advanced cancer patients than in healthy people. 2) The T cell-immune score of patients at stage zero before surgery was comparable to that of healthy controls but patients at stage 1 to IV before surgery was significantly decreased. 3) The number of regulatory T cells of patients at stage zero was comparable to healthy controls but at stage 1 to IV it gradually increased with disease progression. 4) Immunological functions were strongly suppressed after surgery, but recovered to the initial level within a month. 5) Immunological functions were slightly up-regulated in many cases 8 weeks after chemotherapy. 6) Monitoring of immune status was useful to prevent patients from suffering opportunistic infections. 7) The infusion of autologous activated T cells effectively enhanced immune status in some cancer patients.
**O9**

### Polymorphisms in Type 1 and Type 2 cytokine genes might play complementary role in pancreatic cancer susceptibility

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Cytokines and other mediators have been implicated in Type 1 inflammatory pancreatic diseases, including pancreatitis, and cancer. We analyzed TNF-α, IFN-γ, IL4-receptor and IL13 functional polymorphisms as risk factors for pancreatic cancer using DNA collected. We studied 27 pancreatic cancer (PC) cases and 70>90 years old controls considering that PC peaks in over 80s subjects. A trend for the increase of +1902GG IL4r and –308AA TNF homozygous genotypes and for the reduction of +874T IFN-γ positive genotypes was observed among cancer patients. Recent findings have demonstrated that all these genotypes might play a role in PC being TNF-α –308A allele associated with chronic pancreatitis the major pre-cancer lesion in PC and +874T IFN-γ regarded as a positive survival factor for non-resectable pancreatic carcinoma. On the other hand the increased frequency of the +1902GG IL4r genotype, that increased receptor function and STAT-6 intracellular signalling, is in a good agreement with the demonstration in an animal model of a NKT cell subset involved in down-regulation of tumor immunosurveillance. In this view our data seem to suggest that not only a genetically determined Type 1 proinflammatory profile, but also alleles regulating Type 2 inflammation might be involved in predisposing to pancreatic cancer.

**O10**

### From bench to bedside and back – the Senieur Protocol and efficiency of anti-influenza immunization in the elderly

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Prophylaxis with vaccines is important in geriatrics as, apart from specific protection, it reduces incidence of potentially fatal infectious complications and exacerbations of existing medical conditions. Post-vaccination protection depends on immunity and therefore markers of its condition may be used to predict efficiency of vaccination. From the practical point of view, a link between some clinical features of the health status and condition of the immunity are desirable. Simple methods of immunity assessment could serve practitioners to distinguish patients at risk of vaccination unresponsiveness. Additional care, necessary to avoid possible complications, would be then given to such patients, in case the vaccination did not protect them. We assessed different aspects of the functioning of immunity in 142 elderly immunized with anti-influenza vaccine in three consecutive seasons. There was a correlation between health status assessed according to the Senieur Protocol and response to the vaccination. Patients classified as Senieurs responded to the vaccine, while Non-Senieurs did not. The most linked with unresponsiveness were features of circulatory and psychiatric diseases. The protocol corresponded with immune parameters as well. Senieurs revealed good humoral (anti-haemagglutinins and anti-neuraminidases) and cellular (cytotoxicity, % of IFNγ- and perforin-producing CD8+ T and NK cells) responses. Impairment in humoral response could be improved in subsequent seasons, which was not the case of cellular response. Interestingly, patients, who improved humoral responses during subsequent immunizations, were characterized by well-preserved cellular immunity (high NK cytotoxicity, high levels of Th1 cytokines and low proportion of CD28-CD8+ T cells). In contrast to first-vaccination responders, the second-vaccination responders were characterized by elevated levels of proinflammatory cytokines and CMV carrier status placing them in Non-Senieur group. The cells which accumulation was associated with unresponsiveness were CD25highCD4+ T regulatory cells. Concluding, detailed clinical data is enough to give the clinicians presumptive information on the condition of the immune system and allows for initial prediction of vaccination efficiency.
Alterations in lineage commitment accompanies hematopoietic stem cell aging

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Hematopoietic aging is accompanied by a wide range of pathophysiologic changes, including anemia, lymphopenia and an increased propensity for development of leukemia. Mouse models are often used to explore the onset of such changes and have suggested that many age-related changes in the hematopoietic system have a stem cell involvement. However, as evaluations of appropriate stem cell function is based on their capacity to give rise to mature progeny, diminished stem cell function with age could alternatively be a reflection of changes in function at precursor levels downstream of stem cells. To explore potential changes in precursor cell function and frequencies with age, we took advantage of recent advances in the prospective isolation of lineage-restricted progenitors, allowing us to describe several features directly associated with hematopoietic progenitor aging. Apart from the well-established lymphoid deficiency of aged stem cells, functional analyses of aged stem cells demonstrated a preferential ability to differentiate into cells of the granulocytic and platelet lineages. By contrast, aging was associated with severe reductions at multiple levels of erythroid differentiation. Our studies demonstrate that changes in lineage preference is a key feature of hematopoietic aging, and studies are currently ongoing to explore whether altered lineage priming already at the level of hematopoietic stem cells might underlie these changes.

Age and severely depressed left ventricular systolic function is associated with impaired mobilization of bone marrow CD34+CXCR4+ cells in acute myocardial infarction

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Stem/progenitor cells are mobilized into peripheral blood early in acute myocardial infarction (AMI). At the same time the expression of tissue-specific markers (cardiac GATA-4, Nkx2.5/CSX, endothelial VE-cadherin, von Willebrand factor) is markedly induced in circulating mononuclear cells. In patients with low left ventricular ejection fraction (LVEF) and high levels of NT-proBNP in acute phase of AMI the mobilization of CD34+/CXCR4+ cells is significantly impaired, however there is no data regarding the long-term follow-up. Aim of the study was to correlate the early mobilization of CD34+CD117+, CD34+CXCR4+, c-met+ cells in patients with AMI treated with primary PCI with parameters of left ventricular function (LVEF, NT-proBNP levels), hematopoietic cytokines, cardiopulmonary exercise test results and age in one-year follow-up. Methods and Results: 60 patients were enrolled. Stem cells numbers and concentrations of NT-proBNP, SDF-1, G-CSF, VEGF, IL-6 and HGF were measured on admission, after 24 h, 7 days and 1 year. Echocardiography was carried out on admission and after 1 year and ergospirometric exercise test after 1 year post AMI. In patients with baseline LVEF > 40% as well as with NT-proBNP levels in the highest tertile the number of mobilized CXCR4+/CD34+ cells on admission was significantly lower in comparison to patients with better LVEF (<40%, P>0.03) and NT-proBNP levels in the lowest tertile (P>0.001). Patients with LVEF >40% 1 year after infarction had lower baseline CXCR4+ cell counts than patients with LVEF<40% on follow-up visit (P>0.03). Baseline number of CXCR4+ cells was positively correlated with LVEF after 1 year (r=0.55; P>0.03) and in multivariate regression was independent predictor of LVEF <40% after 1 year. The peak number of mobilized CXCR4+ cells early in AMI was also significantly positively correlated with the number of circulating CD34+, CXCR4+ and CD117+ cells after 1 year (CD34+: r=0.35, P<0.05; CXCR4+: r=0.38; P<0.03; CD117+: r=0.4, P<0.02) and patients with low baseline CXCR4 counts had lower number of CD34+, CD117+ and CXC4+ cells as well as higher levels of NT-proBNP after 1 year (all P<0.03). The number of stem cells both on admission and at follow-up was significantly lower in patients aged < 50 years in comparison to younger subjects (P<0.05). No significant correlation between baseline stem cells number and exercise test results were found. Conclusion: In older patients with myocardial infarc-
tion and more severely depressed cardiac function the mobilization of CD34+CD117+, CD34+CXCR4+, cells is significantly compromised. Association of age and bone marrow content of CD34+CXCR4+ cells will be discussed along with data form first clinical trial using bone marrow-derived selected CD34+CXCR4+ cells in patients with acute myocardial infarction.

O13

Ionizing radiation provokes premature senescence in human lung fibroblasts that enhance the growth of malignant lung epithelial cells in vitro and in vivo

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Cellular senescence is considered to be a potent anticancer mechanism. However, it has been proposed that senescent stroma cells may enhance the growth of adjacent malignant epithelial cells. Exposure of tumours to repeated low doses of γ-irradiation is a common treatment regime in several tissues. However, the effect of this stress to the neighboring stromal cells and the interaction of the latter with cancer cells have not been adequately investigated. In this study, we have exposed confluent cultures of human lung fibroblasts, derived from normal or cancer-associated regions, to repeated subcytotoxic doses of 4Gy of γ-irradiation. We have found that a single dose immediately activates a DNA damage response, as shown by the activation of the ATM/Chk2/p53/p21WAF1 axis, leading to an intense cell cycle arrest. After a series of doses (total dose approx. 50 Gy), followed by cell subculturing, cellular senescence was accelerated, as shown by morphological alterations, growth arrest, p21WAF1 upregulation and senescence-associated β galactosidase staining. Next, we studied the effect of these prematurely senescent cells on the growth of human malignant lung cell lines (A549, HT-1080 and H1299). Medium conditioned by young and prematurely senescent cells has no major effect on the proliferation of all three cell lines. However, in co-culture studies we have found that the growth of cancer cells was strongly enhanced when cultured on senescent cells. In addition, in immunocompromised (SCID) mice γ-irradiation-induced senescent cells, similarly to replicative senescent fibroblasts, intensely promoted A549 cells to form tumours. These findings support the idea that replicative, or stress-induced, senescence may contribute to tumourigenesis.
N-glycomic changes in blood proteins during human aging: A potential aging biomarker?

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It is well accepted that the N-linked oligosaccharides of glycoproteins play important biological roles by influencing the functions of glycoproteins. They are important for initiation of various cellular recognition signals that are essential for the maintenance of the ordered social life of each cell within a multi-cellular organism. Although many studies reported the importance of the structural changes of glycans during development and disease, little information is available on the changes in glycans during aging. Accordingly, age-related alterations of the glycans could be relevant to understanding the complex physiological changes in aging individuals. As an early step in this direction, we determined the changes in the blood N-glycome during aging in healthy humans, centenarians and in one Werner patient. N-glycan profiling of the human blood glycoproteins on different age groups of healthy persons shows substantial changes with increasing age in three major N-glycan structures. Above 40-50 years of age, there is an increase in under-galactosylated glycans and a decrease in the core fucosylated bi-galactosylated biantennary structure. These three glycan structures are also substantially changed in a Werner patient, to a level comparable or even more pronounced than those observed in a healthy Italian centenarian population. These data show that the glycosylation machineries in both, liver cells and B-cells are affected in a similar way by the aging process despite their highly different nature. The observed changes in the glycan structures are indicative that biosynthetic processes are at the basis of the changes, possibly together with changes in serum clearing of glycan-altered proteins. Our data suggest that measurement of the N-glycan level changes could provide a noninvasive surrogate marker for general health or for age-related disease progression, and for monitoring the improvement of health after therapy.

The N-glycan profile may be especially interesting for testing the effects of dietary compounds and/or medications on the global health status of an animal, including humans. In a similar way, the N-glycan profile can be used to test the effects of chemical compounds on the global health status.