Plenary lecture

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DEFICIENCIES IN DNA REPAIR AND ITS CLINICAL IMPACTS

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All organisms have evolved an intricate network of DNA repair systems, that permits elimination of virtually any type of DNA injury. Genetic defects in DNA repair pathways or in damage-induced cell cycle arrest result in genetic instability and a strong predisposition to cancer. Examples of this class of human syndromes are xeroderma pigmentosum (XP), Bloom's syndrome, Fanconi's anaemia, and ataxia telangiectasia.

One of the major damage repair pathways is nucleotide excision repair (NER). This system removes a broad spectrum of DNA lesions among which the main UV-induced injury and bulky chemical adducts. Three NER-deficient human syndromes characterized by marked photosensitivity are known: XP, Cockayne syndrome (CS) and trichothiodystrophy (TTD). XP patients show pigmentation abnormalities and an over 1000× increased risk of skin cancer caused by defects in one of at least 7 genes (XPA to XPG). CS displays sun sensitivity and overall developmental impairment. Two responsible genes are known: CSA and CSB. TTD is characterized by brittle hair, ichthyosis and many CS symptoms. The NER defect in TTD is due to mutations in TTDA, XPB or XPD. There are no indications for an increased risk of cancer in CS and TTD. Some patients show a combined XP + CS picture. They have been assigned to XPB, XPD or XPG.

Several of the protein (complex)es involved in NER participate in other DNA transactions as well. The XPF/ERCC1 complex probably has a dual involvement in a mitotic recombination pathway. All three NER genes associated with TTD are also implicated in basal transcription. This notion has important clinical implications. It is likely that the TTD symptoms not explained by a NER defect are caused by subtle insufficiencies in basal transcription. Thus TTD may represent a combined 'repair/transcription syndrome'.

To analyze the complex geno-phenotype relationship between mutations in NER genes and the clinical symptoms we have utilized gene targeting in mouse embryonal stem cells, to generate mouse mutants carrying defined genetic changes in various repair genes. The mouse models provide valuable tools for studying the relationship between molecular defect and clinical symptoms, including cancer predisposition.

Award lecture

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FROM ADJUVANT TO NEOADJUVANT CHEMOTHERAPY FOR HIGH-RISK BREAST CANCER

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During the past quarter of this century numerous efforts were undertaken to identify high-risk women with resectable breast cancer who need either adjuvant or neoadjuvant chemotherapy or both modalities to improve relapse-free and total survival rates. The first prognostic variable taken into consideration to test the value of adjuvant chemotherapy was the pathologic involvement of axillary lymph nodes. The 20-year results of the CMF (cyclophosphamide, methotrexate and fluorouracil for 12 monthly cycles) trial confirmed the preliminary observations of the effectiveness of the treatment in women with node-positive breast cancer, and stressed in both pre and post-menopausal groups the importance of the optimal dose administered (*N Engl J Med* 1995). In subsequent randomized studies the 12-year results of adjuvant CMF proved to be equally effective when delivered for 12 or 6 monthly cycles, and were superior to locoregional therapy alone in women with node-negative and receptor-negative tumors. In recent trials carried out in patients with more than 3 positive nodes, the sequential administration of full dose adriamycin (4 cycles) followed by intravenous CMF yielded superior relapse free and total survival rates at 10 years compared to the alternating administration of adriamycin and CMF (*JAMA*, 1995). The importance of dose size and dose intensity was also evaluated within the context of autologous bone marrow transplantation in the subset of patients with 10 or more positive nodes (*Proc ASCO*, 1995). More recent studies have involved the use of neoadjuvant (primary, preoperative) chemotherapy in women with resectable tumors >3 cm in largest diameter. In this subset, several drug regimens delivered for 3–4 cycles could spare mastectomy in 80% to 90% of women. Furthermore, the 5-year results showed a correlation between primary tumor response to chemotherapy and patient outcome, i.e. response to distant micrometastases (*CA*, 1995). Future trials should test how to properly integrate primary and adjuvant chemotherapy.