143 INVITED

The cell–matrix interaction in sarcoma

I. Stamenkovic. *Switzerland*

Abstract not received.

144 INVITED

Chondrosarcoma subtyping: a hobby for the pathologist or important to find therapeutic targets?

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Conventional chondrosarcoma of bone constitutes approximately 90% of all chondrosarcomas. Conventional chondrosarcomas can be categorised according to their location in bone. The vast majority (>85%) is designated as primary central chondrosarcoma based on their location centrally within the medullar cavity. A minority (up to 15%) of conventional chondrosarcomas develop from the surface of bone as a result of malignant transformation within the cartilage cap of a pre-existent osteochondroma and is therefore called secondary peripheral chondrosarcoma. While central and peripheral chondrosarcoma are histologically similar, at the molecular genetic level they differ. EXT, the gene causing Multiple Osteochondromas, is involved in the origin of osteochondroma and peripheral chondrosarcoma. In central cartilaginous tumours EXT is not involved and the initiating event is still unknown. In addition, central and peripheral chondrosarcoma differ in their chromosome content and in the activity of signaling cascades. Therefore, when the biology of these two subtypes will be further unraveled, different targets for therapy may emerge enabling the design of future tailored therapy for central and peripheral chondrosarcoma.
In addition to conventional chondrosarcoma, several rare subtypes of chondrosarcoma are discerned, together constituting approximately 10% of all chondrosarcomas. Mesenchymal chondrosarcoma is a highly malignant lesion that can occur in bone and soft tissue of relatively young patients and is characterized by scattered areas of differentiated cartilage admixed with undifferentiated small round-cells. Dedifferentiated chondrosarcoma is a highly anaplastic sarcoma next to a (usually low-grade) malignant cartilage-forming tumour, with a remarkably sharp junction between both components, bearing an ominous prognosis. Clear cell chondrosarcoma is a tumour of low-grade malignancy characterized by tumour cells with clear, empty cytoplasm. Periosteal chondrosarcoma arises from the external surface of bone and is possibly of periosteal origin. The few molecular genetic studies on these rare chondrosarcoma subtypes reported so far suggest different molecular backgrounds for each subtype. Thus, chondrosarcoma subtyping is at present not only essential to estimate prognosis for optimal therapeutic decision making, it is also highly relevant to enable the identification of targets for the design of future adjuvant therapy since chondrosarcoma is notorious for its resistance to conventional chemo- and radiotherapy.

Special session (Wed, 26 Sep, 13:30−14:30)
Genetic predisposition to melanoma: from the gene to the patient and vice-versa

145 INVITED

Genetic predisposition to melanoma: high and low-risk genes and how to assess risk in the clinic

J. Newton Bishop[1], N. Gruis[2], Melanoma Genetics Consortium[3]. [1]*Cancer Research UK, Genetic Epidemiology Division, Leeds, United Kingdom;* [2]*Leiden University Medical center, Skin Research Laboratory, Leiden, The Netherlands;* [3]*GenoMEL, www.genomel.org, International, United Kingdom*

Background: The melanoma genetics consortium GenoMEL is comprised of groups from around the world who are working to understand the genetics of susceptibility to melanoma, and how the susceptibility genes interact with the environment. www.genomel.org.
GenoMEL pool data from groups across Europe, Australia, North and South America. The aims are to:
1. Establish the gene penetrance for the most common high risk susceptibility gene, CDKN2A
2. Understand the risk of other cancers in gene carriers
3. Understand the relationship between susceptibility genes and particular patterns of sun exposure
4. Understand somatic events in primary tumours and to understand the impact ot germline CDKN2A mutations on the somatic mutations in primary tumours.
5. To find new high and intermediate susceptibility genes for melanoma
6. To develop risk alogorithms for melanoma based upon meta-analyses of large melanoma case-control studies
7. Understand the determinants of behaviour in the sun so that suitable advice for protection can be included in the risk algorithm.

Results: Germline CDKN2A mutations are associated with earlier age of onset of melanoma, the presence of multiple primaries and pancreatic cancer (at least in some countries). Inherited MC1R variants increased gene penetrance. The assessment of risk in the clinic is therefore dependent on these factors. The role of gene testing will be discussed. Use of an on-line sun exposure questionnaire in multiple countries to collect data on attitudes to the sun will be presented.

146 INVITED

Managing melanoma families in the clinic

J. Hansson. *Karolinska University Hospital – Solna, Department of Oncology–Pathology, Stockholm, Sweden*

Background: Approximately 5−10% of melanoma cases occur in families with hereditary predisposition to melanoma. In a minority of such families the melanoma predisposition can be attributed to germline mutations in high risk genes such as CDKN2A or CDK4, but in the majority the predisposing genetic alterations are unknown. Programmes aimed at providing primary and secondary prevention to melanoma families have been established. The outcome of such activities is illustrated by a preventive program aimed at Swedish melanoma kindreds
Materials and Methods: In 1987 a program was initiated by the Swedish Melanoma Study Group with the aim to provide preventive surveillance to melanoma families. The program is carried out in 12 specialized outpatient clinics. All newly diagnosed melanoma cases are questioned regarding heredity and if additional melanoma cases are verified a pedigree is constructed and family members are invited through the proband to participate in the program. Participating family members are given information on sun protection and skin self-examination. Whole-skin examinations including photographic documentation and dermoscopy are performed with 6-monthly intervals. Nevi with changing appearance, as well as lesions that raise suspicion of melanoma development for other reasons, are excised for histopathologic examination. Genetic testing for germline CDKN2A mutations was performed as part of research protocols.
Results: Between 1987 and 2001 2,080 members of 280 melanoma families were followed. During follow-up 1,912 skin lesions were excised. Of these 53% were common nevi and 40% dysplastic nevi. In total 41 melanomas were removed in 32 individuals: 15 (37%) were in situ melanomas while 26 (63%) were invasive, with a median tumor thickness of 0.5 mm. Of the 32 patients diagnosed with melanoma during follow-up 21 (66%) had had at least one previous melanoma removed. All melanomas except one were diagnosed in families with two or more first degree relatives with melanoma. Diagnosis of melanoma occurred in 3 of 8 kindreds with germline CDKN2A mutations, supporting that this mutation is associated with a high risk for melanoma.
Conclusions: A coordinated program aimed at detecting and offering preventive activities in kindreds with hereditary cutaneous melanoma results in a low incidence of melanomas during the follow-up period and tumors that do arise have favourable prognostic characteristics.

147 INVITED

Phenotypic variation in familial melanoma: a handicap for offering DNA diagnosis to families

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Familial melanoma (FAMMM syndrome) has been defined as the occurrence of two first degree relatives with invasive melanoma, or three or more melanoma patients on the same side of the family. Familial melanoma has similar characteristics as other familial cancer syndromes: tumors occur at younger ages, multiple primary tumors are frequent and a spectrum of other cancers types show increased incidences in the syndrome.
Today there are two major melanoma associated genes, one tumor suppressor gene and one oncogene with mutations already present in the germline, that cause hereditary melanoma: CDKN2A (chromosome 9p21) with gene products p16 and p14ARF and CDK4 gene (chromosome 12q14).
About 40% of all families with multiple melanoma cases (3 cases or more) exhibit a mutation in one of these genes, in the other families yet unknown mutations are supposed to be responsible for the trait.
Families with hereditary melanoma considerably vary with respect to many items, such as the presence of atypical nevi (AN), numbers of AN, the age at which melanomas start developing, the risk of and maximum number of multiple melanomas and the presence of other cancer types (specifically pancreatic carcinoma)

Also in families with exact the same mutation differences in pentrance and expression can be observed. In Leiden a large founder population is present showing a specific 19 basepair deletion called P16-Leiden and even these families show variation in nevus phenotypes and the association with pancreatic carcinoma. In part these variations may be explained by the presence or absene of risk modifying genes like genes for skin type, hair color, sun sensitivity etcetera. Also the presence or absence of genes involved in the formation of moles ("nevus genes" are not yet identified) may interact with the final phenotype of the patiënt. We have observed that P16- Leiden negative family members may show increased numbers of AN, indicative of nevus genes segregating in the family apart from the P16- Leiden mutation.
These observations of variable phenotype and uncertain cancer risks (and the very low yield of mutations in 2 case families) has lead to the opinion of the International Melanoma Consortium not to recommend DNA testing to patients and families.
Since the penetrance figures for the P16-Leiden mutation are fairly well known we have decided to start offering DNA testing to these families in a research setting. Non-mutation carriers are kept in the yearly skin screening if they exhibit 5 or more AN. Psychological studies are being carried out to study the impact of knowledge of gene carriers about their increased pancreatic cancer risk, a disorder for which no screening is possible and no preventive messures are known.

148 INVITED

Genetic predisposition in Spain and Latin America

S. Puig. *Hospital Clinic Barcelona, Melanoma Unit/Dermatology Department, Barcelona, Spain*

Introduction: The Genetics of Melanoma network is a non-profit international consortium (GenoMEL) focused in studies of melanoma genetic susceptibility in Europe, Australia, North America and Israel. Nowadays GenoMEL is obtaining samples and data from an even wider geographical and ethnical spread of familial melanoma in Latin America.
Objective: To study the well-known genes for melanoma (MM) susceptibility (CDKN2A/p14arf, CDK4, MC1R) in familial and multiple primary MM in Spain and Latin America.
Material and Methods: Patients with genetic susceptibility for MM (familial and multiple primaries) from Spain and Latin American countries and Sporadic melanoma cases from Spain were included. Genetic studies, clinical fenotyping and specific follow-up of a subgroup of patients are performed.
Results: CDKN2A mutations were identified in 30% of families, 10% of multiple primaries and 1% of sporadic cases. CDKN2A mutations are responsible of MM susceptibility in a substantial percentage of familial MM patients in Latin American countries. Some CDKN2A mutations have a founder effect: G101W or 358delG originated in Mediterranean countries and −34G>T originated in United Kingdom, some of them were detected in Latin American families. Other CDKN2A missense mutations were detected in Mexican families like I49T described in North America and M52T not previously described. One melanoma patient was homozygote for the I49T mutation in Mexico. The nonsense germline E88X CDKN2A mutation was detected in two not related Uruguayan families. MC1R gene modifies the penetrance of CDKN2A in Spanish population. In multiple primaries the risk to be carrier of a CDKN2A mutation increases with number of primaries, early age of onset and presence of familial history of melanoma. In sporadic melanomas, CDKN2A mutations were associated with gender (males), early age of onset and multiple primary melanomas. An specific follow up programme including total body photography, dermoscopy and recently confocal microscopy permits the diagnosis of early melanomas in high risk patients.
Conclusion: Knowledge on the genetic epidemiology and surveillance programmes of melanoma is of great interest and will contribute for an efficient and reliable management of high risk melanoma patients in Spain and Latin American countries.

Symposium (Wed, 26 Sep, 14:45−16:45)
The challenge of treating advanced pancreatic cancer from translational to clinical trials

149 INVITED

Are there rational novel targets for pancreatic cancer therapeutics? Observations from the M.D. Anderson Cancer Center SPORE in Pancreatic Cancer

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The recent failure of two large randomized phase III trials of the targeted monocloncal antibodies bevacizumab and cetuximab and the limited value of erlotinib has emphasized that therapy for advanced pancreatic cancer remains suboptimal. For this disease it now appears that therapeutically targeting individual proteins involved in the growth of pancreatic cancer cells will only lead to minor incremental improvements in patient survival. What should be our collective response to this fact? The pancreatic cancer SPORE at the M. D. Anderson Cancer Center is attempting to exploit aspects of pancreatic cancer molecular biology in order to discover and evaluate new targets for therapeutic development. Three general approaches are being taken: (1) Understanding the molecular biology of transcription factors activated pancreatic cancer and developing means to inhibit them. Thus far, we have analyzed NFκB and Specificity (Sp) proteins. NFκB has been targeted using the natural product curcumin with promising early activity documented in a pilot clinical trial. Sp proteins regulate many downstream proteins critical to cancer development and growth, including vascular endothelial growth factor. Non-steroidal anti-inflammatory agents such as celecoxib and tolfenamic acid promote proteasomal degradation of Sp1, Sp3, and Sp4 and will be assessed in future clinical trials. (2) Pancreatic cancer cells appear to be particularly susceptible to endoplasmic reticular (ER) stress and cellular proteotoxicity. ER stress can be induced in pancreatic cancer cells using the FDA-approved agent bortezomib. The proteotoxicity of bortezomib against pancreatic cancer cells appears to be due to the failure of bortezomib to stimulate the phosphorylation of PERK, leading to hypophosphorylation of eif2a. Despite bortezomib's inhibition of protein degradation through inhibition of the proteosome, eif2a allows protein translation to continue leading to cellular proteotoxicity. Combinations of bortezomib and protein disrupting agents such as SAHA or specific HDAC inhibitors appear particularly effective in stimulating apoptosis in pancreatic cancer cell lines in vitro and in vivo. A clinical trial assessing this therapeutic approach is underway. (3) Finally, new targets for pancreatic cancer are needed. We are therefore using a novel synthetic lethal screen in Drosophila to identify new targets that will then be evaluated and exploited in vertebrate systems. It is our belief that our efforts to develop new treatments for pancreatic cancer need to be closely integrated with the global efforts to understand the molecular biology of this disease and that future strategies should be rationally designed rather than empiric.

150 INVITED

Trial design issues in advanced pancreatic cancer

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Background: Progress has been slow in pancreatic cancer treatment. Although tumour biology is likely most important for this, design issues may contribute.
Methods: Reports of clinical phase II and III trials in major oncology journals during the past 10 years were scrutinized for aspects that could have influenced the treatment results. Some of these aspects will be discussed.
Results: The results of the many phase II trials, particularly in the locally advanced cases, are often more dependant upon patient selection than treatment efficacy. Since the gains in chiefly survival have been limited, the problems with sufficient power were of concerns, although lately several adequately powered phase III trials have been concluded. It could then be discussed whether some of the gains, shown to be statistically significant, are clinically meaningful considering toxicity and costs. It has been discussed whether patients with locally advanced disease only should be included with those with metastatic disease in trials evaluating systemic treatments. In phase II trials, this can heavily biaz the results, but stratification in the phase III trials can overcome the problem. Evaluation of