IMIG

International Mesothelioma Interest Group

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EDITORIAL

The International Mesothelioma Interest Group was formed in September of 1991 by a group of interested medical practitioners and scientists from different countries whose aim was to improve communications and collaborations amongst workers interested in mesothelioma and asbestos-induced mesothelial changes. Our primary aim was to hold an International Mesothelioma Conference on alternate years, and to share resources.

The second annual mesothelioma meeting was held in May of 1993 as a satellite to the American Thoracic Society Meeting in San Francisco. A summary of the proceedings of this meeting is included. The next meeting will be held in Europe in 1995, possible as a satellite to the European Respiratory Society Meeting in Barcelona (September 24-28), although this has yet to be confirmed.

Included also in this newsletter is a summary of human malignant mesothelioma cell lines which have been described in the literature.

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REPORT OF 2ND INTERNATIONAL MESOTHELIOMA INTEREST GROUP WORKSHOP

SAN FRANCISCO, USA, MAY 1993

Mesothelioma Biology

The current status of oncogenes, tumour suppressor genes and growth factor abnormalities in mesothelioma was discussed. Van Marck (Belgium) assessed N-ras, fos and myc oncoproteins immunohistochemically in mesothelioma and non-neoplastic mesothelium and demonstrated that these proteins were expressed in both tissues. Rb protein, possibly in a mutated form, was found in all mesothelioma cases (nuclear in 75%) and approximately 25% of mesothelioma cases were immuno-reactive for P53 protein (nuclear staining) in contrast to non-neoplastic mesothelium (normal or hyperplastic) which was negative.

Versnel (The Netherlands) studied the presence of PDGF protein immunocytochemically (using a MoAb recognizing AA, AB and BB) in mesothelioma effusions and demonstrated PDGF in macrophages and mesothelioma cells. Double immunofluorescence staining (using EMA) confirmed that mesothelioma cells expressed PDGF. PDGF production by mesothelioma cells

was also demonstrated in tissue sections of each of the three different histological types of mesothelioma, confirming the in-vivo production of PDGF by this tumour. Reactive mesothelium was not totally negative but showed weaker staining.

Robinson (Australia) reviewed the status of his group's work in this area. They demonstrated mRNA for PDGF A and B chains in most mesothelioma cell lines from both humans and mice but anti-sense oligonucleotide inhibition studies demonstrated marked growth inhibition with PDGF A-chain anti-sense oligonucleotides in contrast to those directed at the B-chain. Similarly, anti-sense oligonucleotides against the A-chain receptor were also inhibitory in contrast to those against the B-chain receptor. Similar results were observed using anti-sense oligonucleotides against TGF-β and the data suggests co-operation between TGF-β and the PDGF system. P53 lesions were found in approximately one third of cell lines, consistent with previous data. Transfection of a mutant human mesothelioma cell line with an inducible (metallothionine) wild-type P53 gene induced marked growth inhibition when gene expression was induced.

Masahiko (Japan) evaluated the expression of c-myc, H-ras, c-erb-2 in mesothelioma by immunohistochemical studies and demonstrated expression in 46%, 7% and 13% of cases respectively.

Carbone (USA) injected hamsters with SV40 and evaluated mesothelioma development. Interestingly, 50% of hamsters injected via the intracardiac routes developed mesothelial tumours, in all of which the SV40 gene was integrated and expressed. None of the hamsters injected with SV40 t-deletion mutants developed mesothelioma. Both epithelial and spindle tumours occurred in these animals (at different parts of the tumours) indicating mixed pathology. Tumours developed 3-6 months after injection. Other animals developed lymphoma. It is intriguing that this virus can induce the development of mesothelioma in-vivo (in the context of its ability to transform mesothelial cells in-vitro) and it is intriguing that an intracardiac injection of this virus will induce mesothelioma in 50% of animals.

Mossman (USA) evaluated c-fos and c-jun proto-oncogene expression in rat pleural mesothelial cells and hamster tracheal epithelial cells after exposure to crocidolite or chrysotile asbestos. Asbestos induced a persistent increase in expression in these genes particularly crocidolite. The data suggests that asbestos-induced carcinogenesis may occur though chronic stimulation of cell proliferation via the early response gene pathway including c-jun and c-fos.

Broaddus (USA) demonstrated production of IL-8 (a neutrophil chemotactic factor) by mesothelial cells in-vitro and in the pleural space in-vivo following installation of crocidilite in rabbits and, by antibody inhibition, demonstrated that IL-8 contributed most of the neutrophil chemotactic activity in this model.

Everitt (USA) evaluated mesothelioma induction by man-made mineral fibres following inhalation. Mesothelioma incidence was 3% in rats and 42% in hamsters, the latter possibly being due to the presence of a more reactive mesothelium.

Rodriguez-Panadero (Spain) evaluation the pleural coagulation and fibrinolytic system during talc pleurodesis and showed and increase in pleural coagulation and fibrinolysis, with a fall in

D-Dimer levels in those who achieved good results with talc poudrage.

Immunobiology

Haddada (France) described a replication-defective recombinant adenovirus harbouring the murine IL-2 gene under the control of a viral promoter and its expression in non-dividing tumour cells. These cells induce systemic anti-tumour reactivity. The in-vivo transfer of these constructs to subcutaneous tumours showed effective transfer with some effect on tumour progression and clinical trials are planned.

Robinson (Australia) summarised their group's work evaluating the efficacy of stable transfection of allo MHC molecules (class I) into murine tumours and the capacity of this to induce a protective immune response against untransfected cells. Limited protection could be achieved using the class I allo transfectants.

Mutti (Italy) demonstrated ICAM-1 expression on reactive mesothelial cells from serous effusions. This group also demonstrated TNF-α release by a mesothelioma cell line following LPS stimulation. They suggest that this finding has implications when TNF as potential therapy is considered. It may also have implications for understanding the systemic symptoms suffered by patients with this disease.

Nakano (Japan) demonstrated elevated serum IL-6 levels in mesothelioma with some correlation between IL-6 levels and platelet counts. Immunohistochemical staining of biopsy tumour tissue was positive for IL-6. Van Hezik (The Netherlands) also found elevated IL-6 levels in mesothelioma in the serum and in the pleural fluid of patients with mesothelioma but with little correlation with blood platelet count. In contrast he found a strong correlation between soluble IL-2 receptor in the serum and platelet count.

Epidemiology

Musk (Australia) followed up the unique cohort of non-occupationally exposed residents from Wittenoom (exposed to crocidolite). From a cohort of 4,890 residents 24 have developed mesothelioma (9 males, 15 females), with time from first exposure to diagnosis ranging from 23-44 years and a period of residence (ie. exposure ranging from 6 weeks to 11 years).

McDonald (UK) summarised the mortality from mesothelioma in Quebec chrysotile miners and millers. He confirmed the higher death rate but was unable to resolve the issue yet of the attributability of contaminating fibrous tremolite.

Ekholdt (Norway) described a successful co-operation between mesothelioma interests groups in Norway, Sweden and Finland, establishing standards for diagnosis, treatment and response evaluation.

Clinical/Therapy

Donna (Italy) described an anti-mesothelial antibody, reactive against normal and mesothelioma cells, generated from human antigen isolated from malignant effusions.

Galateau-Salle (France) used a variety of antibodies to evaluate immunohistochemical diagnoses of mesothelioma. They found that dual negativity to CEA and LeuM1 favoured mesothelioma and focal staining with LeuM1 favoured adenocarcinoma. However no commercially available marker differentiated atypical mesothelial