

EDITORIAL

Focus on mesothelioma and the mesothelial cell

M-C. Jaurand*, J. Bignon

Diffuse malignant mesothelioma (DMM) is a tumour which arises from cells of mesodermal origin layering the surface of the thoracic and abdominal serosal cavities of the body. All epidemiological studies indicate that its incidence is increasing in males in industrialized countries, obviously in direct relation with past occupational exposure to asbestos [1-3]. However, it is now well demonstrated that other mineral fibres may induce DMM [4], and in addition, some synthetic fibres in small rodents [5]. Although past occupational exposure to asbestos is presently the main causal factor of DMM in man, it remains that no exposure is found in about 1/3 of cases, as illustrated by the case-control study presently carried out in France.

Two major problems are associated with DMM. First a difficult diagnosis [6]. *In fine*, the definite diagnosis of DMM is based on histological examination, by trained pathologists, using immunohistochemical stainings [7]. Second, a poor prognosis since all classical treatments, surgery, radiotherapy as well as chemotherapy, have demonstrated their ineffectiveness in DMM. Because of these different issues, many studies have been performed throughout the world to help improve the knowledge on DMM but no scientific event had given the opportunity for clinicians and scientists to gather together to discuss the past and new data on DMM. Indeed, up to now, the problems related to DMM were mainly considered during workshops related to asbestos effects.

It was thus decided to organize a conference focusing on all aspects of the biology of DMM. This was held in Paris between September 30-October 2, 1991; it gave the opportunity for several teams involved in research on mesothelial cells and mesothelioma to meet. The proceedings of the conference appear as issue No. 11 of the European Respiratory Review [8], where the reader will find the summary of the past data and recent information concerning the histogenesis, pathogenesis, epidemiology, cell biology and molecular biology of mesothelioma. During this meeting, several points were stressed, based on recent developments of research.

Regarding the accuracy of the pathological diagnosis, the most discriminative markers seem at present to be the presence of keratin and vimentin contrasting with the absence of carcinoembryonic antigen (CEA) [7]. However, the use of specific monoclonal antibodies against mesothelioma cell membrane antigens must be encouraged, in order to allow a better discrimination between DMM and

adenocarcinoma [9]. Transmission electron microscopy may also help to reach the exact diagnosis.

Serum markers such as hyaluronan, tissue peptide antigen and possibly other proteins have to be investigated in order to see if they can identify the early stages of the disease, particularly in subjects, with past occupational exposure to asbestos, "at risk" of developing mesothelioma.

DMM is usually associated with a pleural and alveolar lymphocytosis, and with an increase of CD4 and CD4/CD8 ratio in the pleural fluid. However, other immunological changes (NK cells, cytokines) have to be assessed in order to better seize the basis of immunotherapy [10].

As a prerequisite to new treatments, the methodology of therapeutic trials has to be clearly defined. The low frequency of DMM implies the need for multicentric studies. Furthermore, an accurate evaluation of the responses to treatment is needed. CT scan and thoracoscopy are the main tools for staging the disease [11]. Such methodological standardisation has been reached in the French trial using intracavitary injections of IFN γ as reported during the conference. This trial has shown that the responses to treatment were only observed in limited tumours (stage IA, IB, and IIA) [12]. However, in the absence of an untreated randomized control group, it is difficult to differentiate the effect of the drug *versus* the effect of the stage of the disease.

As DMM develops in a closed cavity, the intraserosal delivery of therapeutic agents has several advantages: less systemic diffusion of toxic drugs, local immune stimulation, higher concentrations in direct contact with tumour cells. This is particularly suitable for immunotherapy using high molecular weight recombinant cytokines, such as interferons or interleukin-2, which have limited or no access to the pleural or peritoneal cavities after systemic injection. This local therapeutic strategy will be particularly appropriate for the future development of advanced gene therapy protocols. Before applying this therapeutic approach to human cases, animal and cell models are necessary for the development and comprehension of these new strategies.

Studies based on cell and molecular biology are important to determine the functions of mesothelial cells and the mechanisms of mesothelial cell transformation; they are also useful in assessing the mechanisms and effects of drugs that may be used for therapeutic purposes.

In the past, mesothelial cells were often considered as a passive cell layer; at present, they appear to play a role in inflammatory processes. These functions will be

* Unité Inserm U 139, CHU Henri Mondor, F-94010 Creteil, Cedex, France

better known in the near future [13]. The main interest in studying mesothelioma cell lines is, not only to better characterize tumour cells, but also to have a tool for investigating pathogenesis and response to drugs. The analysis of mesothelioma cells has revealed a great range of abnormalities: a phenotypic polymorphism has arisen from structural and ultrastructural studies of cell lines which, however, is not associated with great changes in antigenic specificities (as regards vimentin, keratin and CEA content). Many questions remain to be solved on the significance of cell differentiation. Karyotypical analyses of mesotheliomas have also revealed numerous and a large range of chromosome abnormalities [14, 15]; no specific changes were detected in spite of non-random modifications such as excess of chromosomes 5, 7, 20 and loss of 22. Are those dependent on etiological factors and/or individual genetic factors? Why does mesothelioma exhibit such a variety of changes when diagnosed? Is this related to a very rapid progression from the time of fixation of the neoplastic state? All these questions will find answers in the following years, especially with use of cell lines.

Neoplastic cell transformation is associated with changes in cell growth control, producing a growth advantage to neoplastic cells. Platelet-derived growth factors seem to play a critical role in these processes since an abnormal expression of the relevant genes in comparison with normal cells has been reported in man [16]. No specific oncogene activation/tumour suppressor gene inactivation has so far been detected in human mesothelioma, a situation which might be different in rodents. Further research needs to be performed to determine the nature of the genes involved in mesothelial cell neoplasia. Moreover, they might produce an explanation for the occurrence of "familial cases" of mesothelioma.

The discovery of mesothelial changes associated with neoplastic transformation should have an effect on the prevention of mesothelioma, because they would allow prediction of the effects of agents (new fibres, chemicals) that can reach the pleura.

In view of the lack of an efficient cure for mesothelioma, the development of *in vitro* models, either alone or in association with nude or syngenic mice models, is now in progress. It is our hope to see these systems employed to investigate the effects of chemical and immunological molecules on cell proliferation and on tumour growth. Further research should be performed to investigate the mechanisms of drug resistance in mesothelioma.

In the near future, many studies will be carried out with mesothelial cell strains or mesothelioma and mesothelial cell lines. This is a necessary evolution which, however, may pose some problems to extrapolate to the *in vivo* situation, because of the suspected differentiation in long term cultures. Nevertheless, because of the variety of methods for characterizing cell differentiation, many investigations can be made with well characterized mesothelial cells and may, therefore, be relevant.

In the past, the studies have emphasized the problems related to mesothelioma (diagnosis, prognosis, treatment). At present, many investigations have progressed to

better characterize mesothelioma and mesothelial cell transformation. Some clues have been unearthed. However, few studies have been made concerning the metastatic potential of the tumour. We hope that new studies will be instigated which may solve the questions still arising.

Being surrounded these days with many new publications regarding epidemiology, biology and treatment of mesothelioma, we are persuaded that the readers of the European Respiratory Review will find up to date information on the issue of "Mesothelial Cell and Mesothelioma". The large attendance at this first workshop has emphasized the need for co-operative efforts, allowing expressions of multidisciplinary contributions. This meeting provided the opportunity for launching an International Mesothelioma Interest Group (IMIG) which, we hope, will help in the near future to improve prevention, diagnosis, treatment and prognosis of this severe disease.

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