Studies on slow virus diseases of sheep and goats in Israel

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Summary: A review is given of recent research work on slow virus diseases of sheep and goats, and results of studies carried out on these diseases in Israel are presented.

Pulmonary adenomatosis of sheep which exhibits all the criteria included in the definition of bronchiolo-alveolar cell carcinoma is caused by a retrovirus distantly related to the Lentivirus genus.

On the other hand, the etiological agent of caprine arthritis-encephalitis is a distinct member of the lentivirus group of the Retroviridae family of which the maedi-visna virus is the prototype.

I. — INTRODUCTION

The concept of slow virus infections was introduced by Dr. Bjorn Sigurdsson in his classic descriptions of rida, visna, maedi, and infectious sheep pulmonary adenomatosis (SPA) as transmissible chronic diseases of Icelandic sheep (1, 2, 3, 4). This presentation is specifically concerned with pathogenetic and virological aspects of SPA, maedi-visna (MV) and with caprine arthritis-encephalitis (CAE) disease complexes which are distributed worldwide.

II. — SHEEP PULMONARY ADENOMATOSIS (SPA)

SPA, also called jaagsiekte or sheep pulmonary carcinoma (SPC) is characterized by tumor cell growth in the lungs with metastases in the pulmonary and mediastinal lymph nodes (5-13). Metastases in the mesenteric lymph nodes and visceral organs have also been reported (9, 10, 11, 12).

Histopathologically, the neoplastic cells, mainly cuboidal in shape, may be arranged in short rows, layers, acinar or papillary structures which arise from the alveoli, alveolar ducts and bronchiolar epithelium (6, 10, 11, 13, 14, 15). Our ultrastructural examinations (8), followed by others (16), confirmed the origin of the neoplastic cells from the terminal bronchiolar epithelial cells and from type II alveolar epithelial cells (called also type B alveolar cells or granular pneumocytes).

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The overall tumor architecture and the ultrastructure of the neoplastic cells, including the metastasis, warranted the classification of SPA as bronchiolo-alveolar cell carcinoma (13). Epidemiological and experimental evidence indicates that this neoplasm is horizontally transmitted in nature (6, 7, 11).

A decade ago, we first reported that virus particles morphologically similar to RNA tumor viruses (Retroviridae, i.e., clusters of intracytoplasmic A and budding C-type particles) are present in situ in SPC (8). Retroviruses are proved agents of oncogenesis in certain species. Our electron microscopic findings were confirmed more recently by other authors (17).

The observations of the presence of retroviruses were complemented by our findings that extracts of sheep lung tumors contain particles with a density of 1.15-1.20 g/ml having the characteristics of a reverse transcriptase in association with a 60-70S RNA (18). The presence of reverse transcriptase producing agent in SPA was reconfirmed (19). When sheep were given this fraction endobronchially, adenomata developed in two of four inoculated animals (19). More recently, pulmonary adenomatosis was transmitted to newborn lambs by inoculation of the microsomal fraction of a cytoplasmic extract of cultured SPC tumor cells or tumor tissue (20). We have also examined aliquots of equilibrium density gradient-purified material from lung tumor and normal lung tissue by electron microscopy, and tested them for the presence of reverse transcriptase and tumorgenicity. We were able to demonstrate that sections from the 1.15-1.20 g/ml density regions of the tumor material contained reverse transcriptase activity, and possessed morphologically typical C-type « mature » and « immature » retroviruses (18). Normal adult sheep inoculated last year intrapulmonarily with these virus-containing fractions developed the typical proliferating neoplasm after a year (21).

Furthermore, in vitro, preliminary results indicate that extracellular retroviruses are produced when tumor cell samples, obtained from the experimentally diseased sheep, are cultivated with a Himalayan tahr ovary permanent cell line.

In summary, the electron microscopic observation of retrovirus in the lungs of sheep bearing SPC, the detection of particles with reverse transcriptase together with recent infectivity in vivo and in vitro studies indicate a retrovirus etiology of pulmonary carcinoma of sheep.

However, in addition to the retrovirus etiology of SPA, herpes-like particles were found in tissue cultures of alveolar macrophages and lung tissues of SPC diseased animals (22, 23), and this herpes virus could be transmitted to normal cultures (24, 25, 26). Nevertheless, attempts to produce neoplasm with this agent alone have been unsuccessful (19).
III. — MAEDI-VISNA (MV)

Maedi and visna were recognized initially as sporadic diseases of the central nervous system and respiratory system, respectively. It was recently proven through comparative virus morphogenetic studies, molecular hybridization, serological and disease transmission experiments that both disease entities are caused by the same virus and therefore should be referred to as maedi-visna (4, 27-33). The maedi-visna virus has been classified as a retrovirus (RNA tumor virus). It has morphological and biochemical characteristics of the RNA tumor viruses and, moreover, exhibits some oncogenic properties (27, 28). Although RNA tumor viruses are proven agents of oncogenesis in certain species, a variety of spontaneous retroviral diseases in animals initiate chronic degenerative and autoimmune diseases.

In 1981, we reported the first isolation in Israel of a C-type retrovirus from pulmonary lesions from a maedi-visna diseased ewe. The virus isolated exhibited the features characteristic of retroviruses, i.e., its density on sucrose gradients is 1.16 g/ml, it contains a 60-70S RNA and RNA directed-DNA polymerase, and infected cultures contained virus particles morphologically characteristic of Retroviridae which are not present in non-infected cultures. Morphogenesis of the virus is identical to that of the classical maedi-visna (European and U.S.A. isolates). In our laboratory two cell lines, ovine fetal corneal cells and goat ovary cells routinely yield high amounts of this virus.

Lymphoid proliferation in the lungs and/or in the central nervous system and/or in the joints, and lymphoid hyperplasia in lymph nodes and in the spleen are found in maedi-visna disease. The general opinion is that this lymphoid reaction is a response to the infection and not malignant in nature. Takemoto and Stone (27, 28) reported, however, transformation of murine tissue culture cells after infection with maedi-visna virus and virus could be «rescued» from infected cultures by co-cultivation with normal sheep testicular cells, in analogy with the classical work on Rous Sarcoma virus. Though the oncogenic potentialities of the maedi-visna virus are not yet defined, the above-mentioned features of the virus and the pathogenesis induced by its presence, call for further evaluation and are presently being examined by our group.

The relationship between the C-type retrovirus of SPA and the maedi-visna C-type virus was tested by us by molecular hybridization which revealed no sequence homology (34). This indicates that the maedi-visna virus is not implicated in the etiology of SPA, complementing numerous earlier studies in which striking differences in clinical symptoms, pathology, serology (4, 21, 31, 32) and histopathology were found between the two sheep diseases.
IV. — CAPRINE ARTHRITIS-ENCEPHALITIS (CAE)

Previous communications have described the histological and pathological features of CAE, in which, when young goats become infected, a primary phase ensues, featuring demyelination of the central nervous system accompanied by interstitial pneumonia. Survivors of this phase continue to exhibit active lesions for years and often develop arthritis (35, 36, 37). The main histopathological changes found in the joints were synovial cell hyperplasia and lymphocyte and plasma cell infiltration. Progression of the disease is accompanied by degenerative changes such as necrosis, fibrosis, and mineralization of synovial membranes as well as the appearance of periarticular collagenous structures. The manifestations of the lesions in the CNS and lungs are morphologically similar to those found in maedi-visna infected sheep (38, 39, 40).

Cell free transmission of CAE indicated that a viral etiology was likely in this important and widespread disease (34, 35). Recently, evidence was presented that the agent is a retrovirus which is closely related to maedi-visna virus of sheep (40, 41, 42). The virus isolated from the diseased goats exhibits several features characteristic of retroviruses, i.e., its density in sucrose gradients is 1.15 g/ml (identical to maedi-visna), it contains a 60-70S RNA, and RNA-directed DNA polymerase, and infected cultures contained virus particles morphologically characteristic of Retroviridae (43).

In a collaborative preliminary study we compared the morphogenesis of the CAE virus (CAEV) to that of sheep progressive pneumonia virus (maedi-visna, U.S.A. isolate) and presented evidence that the two are similar but not identical (42). Furthermore, we could demonstrate that the goat retrovirus isolate grows in vitro in ovine cell lines as well as in goat cells, as does the Israeli (ovine) maedi-visna isolate (21, 42, 44). These data may indicate that the goat retrovirus may well be a variant of the ovine maedi-visna virus (41, 42). However, nucleotide sequence relationship between the CAEV genome and the genomic RNA of maedi-visna virus, examined by reciprocal cross-hybridization tests in which [3H]-labelled DNA probes, complementary either to CAEV viral genome or to maedi-visna viral genome exhibited only limited sequence homology. These results which show only limited sequence homology between CAEV and MV indicate that this goat virus is a separate virus (45). Although the pathogenesis of CAEV, its morphogenesis and morphology, the shared p30 antigen with MV group — all indicate that this caprine virus is part of the Lentivirus genus of the Retroviridae family (46).

L'ÉTUDE DES MALADIES À VIRUS LENTS DES OVINS ET DES CAPRINS EN ISRAËL. — K. Perk et I. Hod.

Résumé : Les auteurs présentent une synthèse des travaux récents sur les maladies à virus lents des ovins et des caprins ainsi que les résultats des études faites en Israël sur ces maladies.
L'adénomatose pulmonaire du mouton présente toutes les caractéristiques du carcinome bronchiolo-alvéolaire. Cette infection est provoquée par un rétrovirus qui a une parenté éloignée avec le genre lentivirus.

Par contre, l'agent étiologique de l'arthrite-encéphalite caprine est un membre distinct du groupe lentivirus de la famille des Retroviridae dont le virus de référence est celui du maedi-visna.

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EL ESTUDIO DE LAS ENFERMEDADES POR VIRUS LENTOS DE OVINOS Y CAPRINOS EN ISRAEL. — K. Perk y I. Hod.

Resumen: Presentan los autores una síntesis de las recientes investigaciones sobre las enfermedades por virus lentos de ovinos y caprinos, así como los resultados de los estudios hechos en Israel sobre estas enfermedades.

La adenomatosis pulmonar del carnero presenta todas las características del carcinoma bronquioloalveolar. La infección es provocada por un retrovirus que tiene un parentesco alejado con el género lentivirus.

En cambio, el agente etiológico de la artritis-encefalitis caprina es un miembro diferente del grupo lentivirus de la familia de Retroviridae, cuyo virus de referencia es el del maedi-visna.

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REFERENCES


