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Retrovirus-Induced Malignant Histiocytosis in Mice: A Model for the Human Disease

J. Löhler [1], T. Franz [1], K. Klingler [1], W. Ostertag [1], and R. Padua [2]

Malignant histiocytosis, also known as histiocytic medullary reticulosis or malignant reticulosis, is a hematopoietic neoplastic disorder characterized by proliferation of abnormal histiocytes and of their precursors, with mostly a rapidly fatal course [1, 2]. Clinical findings are fever, jaundice, pancytopenia, and enlargement of liver, spleen, and lymph nodes. The etiology of the disease is unknown, although viral infections have been suggested as playing a role [3]. The study of its pathogenesis has been hampered by the lack of a suitable animal model. However, we have recently described a novel retrovirus inducing a systemic neoplastic disease in mice which is strikingly reminiscent of malignant histiocytosis in humans [4].

A new isolate of a murine retrovirus with spleen focus-forming activity – the AF-1 or, as it is now designated, malignant histiocytosis sarcoma virus (MHSV) – was derived from sarcomas that had been induced on passage of a cloned Friend helper virus in newborn BALB/c mice. Subsequently, the transforming defective subunit of the MHSV complex was cloned in NRK cells. Injection of the MHSV into mice revealed its unique capacity to transform macrophage precursor cells. MHSV-sensitive DDD mice (Fv-2^s and Fv-2^r) rapidly develop splenomegaly, hepatomegaly, and pancytopenia after intravenous infection and die within the first 25 days of the disease. Histological examination showed the proliferation of histiocytic tumor cells in bone marrow, spleen, lymph nodes, and liver, with a final infiltration of all major parenchymal organs (Fig. 1). Permanent cell lines established from MHSV-infected DDD or BALB/c mice, histiocytic tumor cells in situ, and cells of serially transplanted tumors all exhibited differentiation-specific antigens, intracellular enzyme patterns, and phagocytic ability characteristic of mononuclear phagocytes (Table 1). Mice

Table 1. Histochemical, immunohistochemical, and functional characterization of histiocytic tumor cells in MHSV-infected DDD mice, and permanent cell lines derived from tumor-bearing DDD mice

	Tumor cells in spleens of DDD mice	Permanent cell lines	
		HA15/A[a]	HA15/S[b]
Non specific esterase	+	+	+
Lysozyme	+	+	+
Alkaline phosphatase	−	−	−
F4/80 antigen	+	+	+
Pan-B-cell antigen	−	−	−
Thy-1	−	−	−
Phagocytosis	+	+	+

[a] Slow-growing adherent cells resembling macrophages.
[b] Predominantly suspended growing cells resembling monoblasts.

[1] Heinrich-Pette-Institut für Experimentelle Virologie und Immunologie an der Universität Hamburg, FRG
[2] Marie Curie Memorial Foundation, Research Institute, The Chart, Oxted, UK

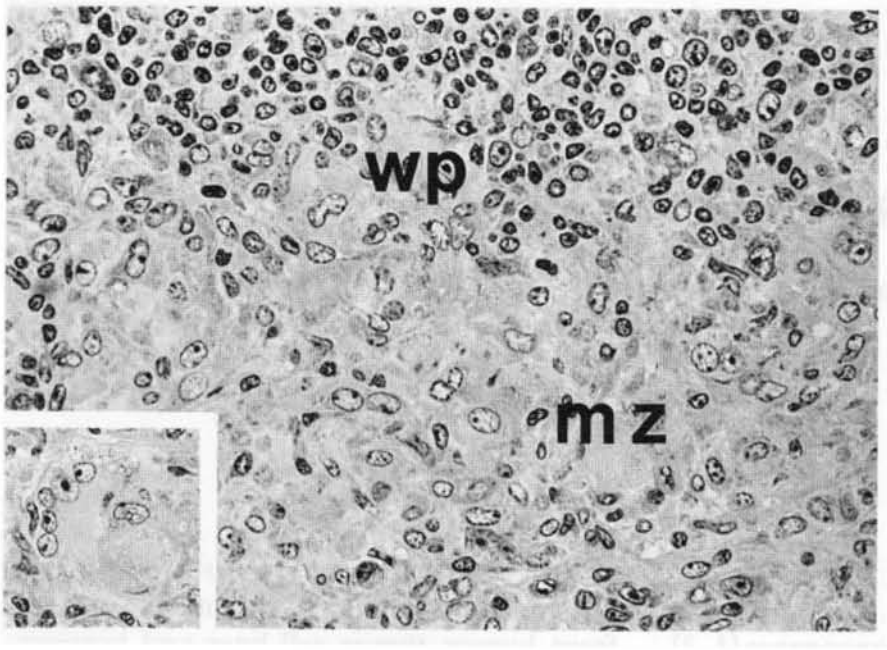

Fig. 1. Spleen of DDD mouse 8 days after infection with MHSV. Proliferation of histiocytic tumor cells in the marginal zone (*mz*) of the white pulp (*wp*). The *inset* shows a multinuclear giant cell. Toluidine blue; ×187

infected with MHSV show a large relative increase in myeloid precursor cells (CFU-C). Examination of these CFU-C in spleen and bone marrow of infected DDD mice showed that the normal distribution of CFU-C (CFU-G 25%, CFU-M 25%, CFU-GM 50%) was shifted toward a predominance of macrophage colonies: approximately 95% of the spleen CFU-C of infected DDD mice were CFU-M. Most of these CFU-C proliferated in the absence of growth factors, which are required for the growth of CFU-M of uninfected animals. Partial nucleotide sequence analysis of molecularly cloned MHSV shows that MHSV has a unique F-MuLV-related long terminal repeat with one large deletion and duplications within the direct repeat. MHSV contains, like Harvey and Kirsten sarcoma virus, rat VL30 sequences, and the *ras* oncogene of MHSV encodes a p21 protein (Padua et al., in preparation).

In conclusion, symptoms and pathological alterations of the histiocytic neoplastic disorder in mice caused by the MHSV share many features with the malignant histiocytosis of man. Irrespective of a possibly different etiology of the human and murine malignancies, we hope that studying this animal model will provide more insight into the mechanisms operating in the pathogenesis of the fatal human disease.

References

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