ANIMAL MODEL OF HUMAN DISEASE

Melanoma

Sinclair Swine Melanoma

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Biologic Features

The Sinclair swine melanoma model system has a vast array of pigmentary abnormalities, including cutaneous melanomas. Grossly, two types of lesions are seen: 1) flat, darkly pigmented lesions representative of junctional nevi comprised of cytologically malignant cells, examples of atypical melanocytic hyperplasia, and 2) raised black lesions that demonstrate an invasive malignant melanoma with an adjacent intraepidermal component analogous to human superficial spreading melanoma.[1] The swine model is characterized by a high incidence (54%) of spontaneous-cutaneous malignant melanomas in newborn progeny derived from parents with melanoma; tumors continue to develop after birth, to produce an incidence of 85% by 1 year of age. Melanomas that develop after birth develop both from flat, darkly pigmented lesions and from skin free of detectable melanocytic lesions.[2] Metastatic spread of malignant melanocytes into the draining lymph nodes is a frequent consequence of the active growth phase of the cutaneous tumor; metastatic invasion of other organs is less frequent but not an uncommon occurrence.[1]

The most unique feature of the melanomas in swine is the spontaneous regression of primary and metastatic lesions that occurs within the first year of life. Spontaneous regression may begin as early as 1 month of age and is characterized by a decrease in tumor volume and sequential changes in tumor pigmentation from black to white. Pigmentation changes are not limited to the tumor and range from a localized depigmentation of adjacent hair and skin to a generalized depigmentation that includes the iris of the eye.[3,4]

Host control of tumor development, growth, and regression in pigs is indicated by both a linear decrease in tumor development and a decrease in tumor growth rate with age.[2,3] Although tumor regression cannot be definitely attributed to a tumor-related immune response, evidence indicates that a tumor-related immune response is associated with tumor growth and regression. This evidence includes 1) a host inflammatory response in regressing tumors that is characteristic of a tumor-related immune response,[1] 2) immunologic assays that demonstrate sensitivity to and recognition of melanoma-associated antigens by melanoma swine lymphocytes stimulated *in vitro* with melanoma-associated antigens,[5,6] and 3) demonstration that lymphocytes from pigs with melanoma are highly cytotoxic for melanoma cells.[6] Preliminary evidence indicates that the strength of the tumor-related immune response can be correlated to tumor growth and regression.

Comparison With Human Disease

The Sinclair swine melanoma model has many features in common with its human counterpart: 1) tumors develop spontaneously; 2) swine possess a wide spectrum of benign melanocytic lesions capable

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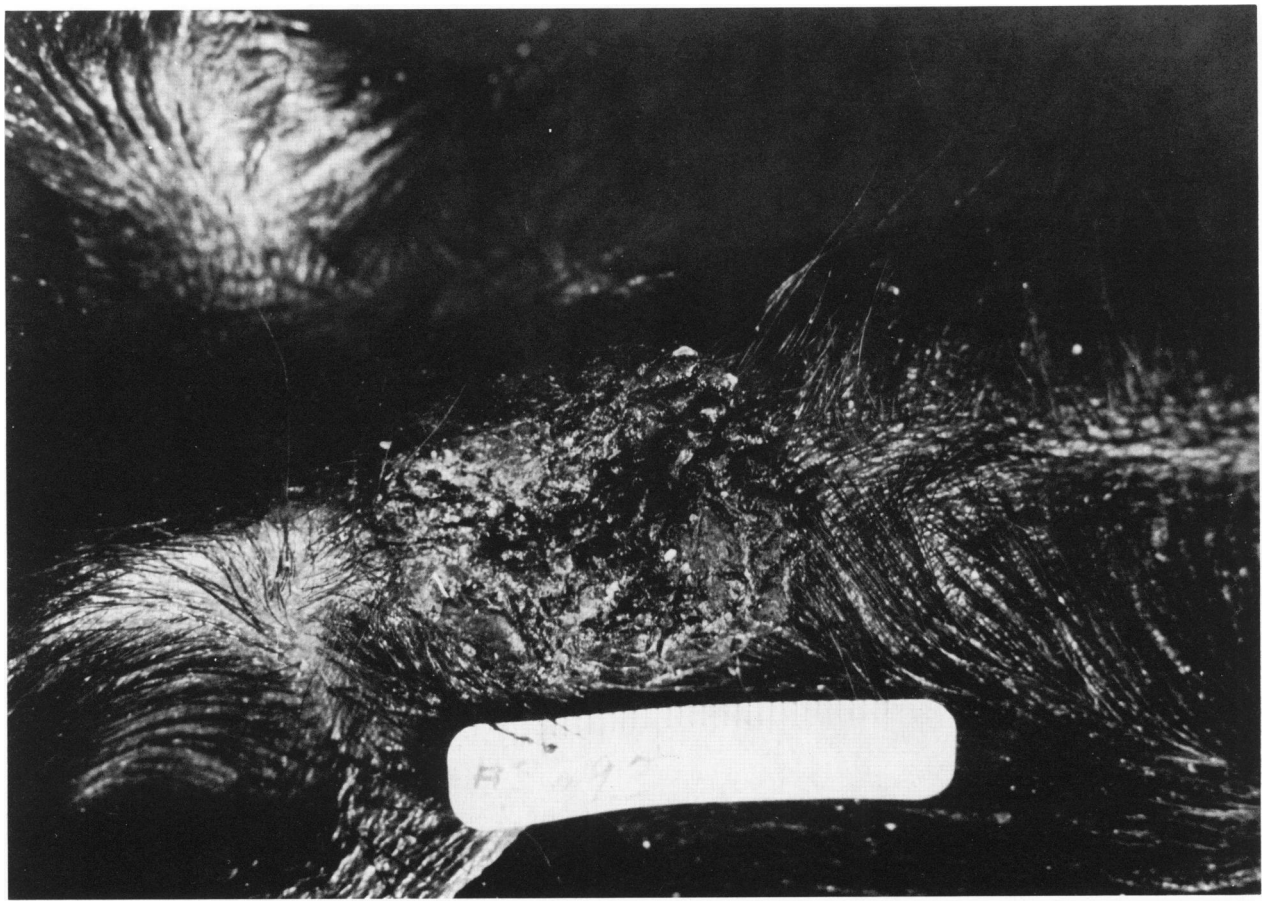

Figure 1 — Large raised melanoma on the abdomen of a 1-month-old pig. Note the ulcerated center exuding melanin.

of malignant transformation; 3) melanomas in pigs histopathologically resemble human superficial spreading melanoma; 4) metastatic disease is correlated with deeply invasive cutaneous tumors; 5) the pattern of metastatic spread is analogous to the distribution of metastases in human melanoma; 6) the histopathology of cutaneous regression is similar; 7) a tumor-related immune response occurs in the host; and 8) a genetic component is readily apparent that is comparable to the genetic component of some melanomas in man.[1-5] However, there are three features that differentiate swine melanoma from human melanoma; 1) melanomas have not been observed in white swine; 2) tumor development is not related to ultraviolet radiation; and 3) complete tumor regression occurs in most swine. Although these differences may somewhat limit the types of studies that can be performed with this animal model, complete tumor regression is a feature that can be exploited.

Usefulness of the Model

Sinclair swine melanoma provides a unique opportunity to investigate host–tumor-cell interactions in a clinically relevant system. The swine melanoma model has many features in common with human malignant melanoma. Furthermore, substantial evidence exists that host immunologic factors play a role in the development, growth, and regression of this neoplasm.[1,5,6]

The Sinclair swine melanoma model also provides an excellent system in which to investigate the progressive cellular changes during the transition from normal, through premalignant, to malignant and metastatic melanoma, as well as the cellular changes

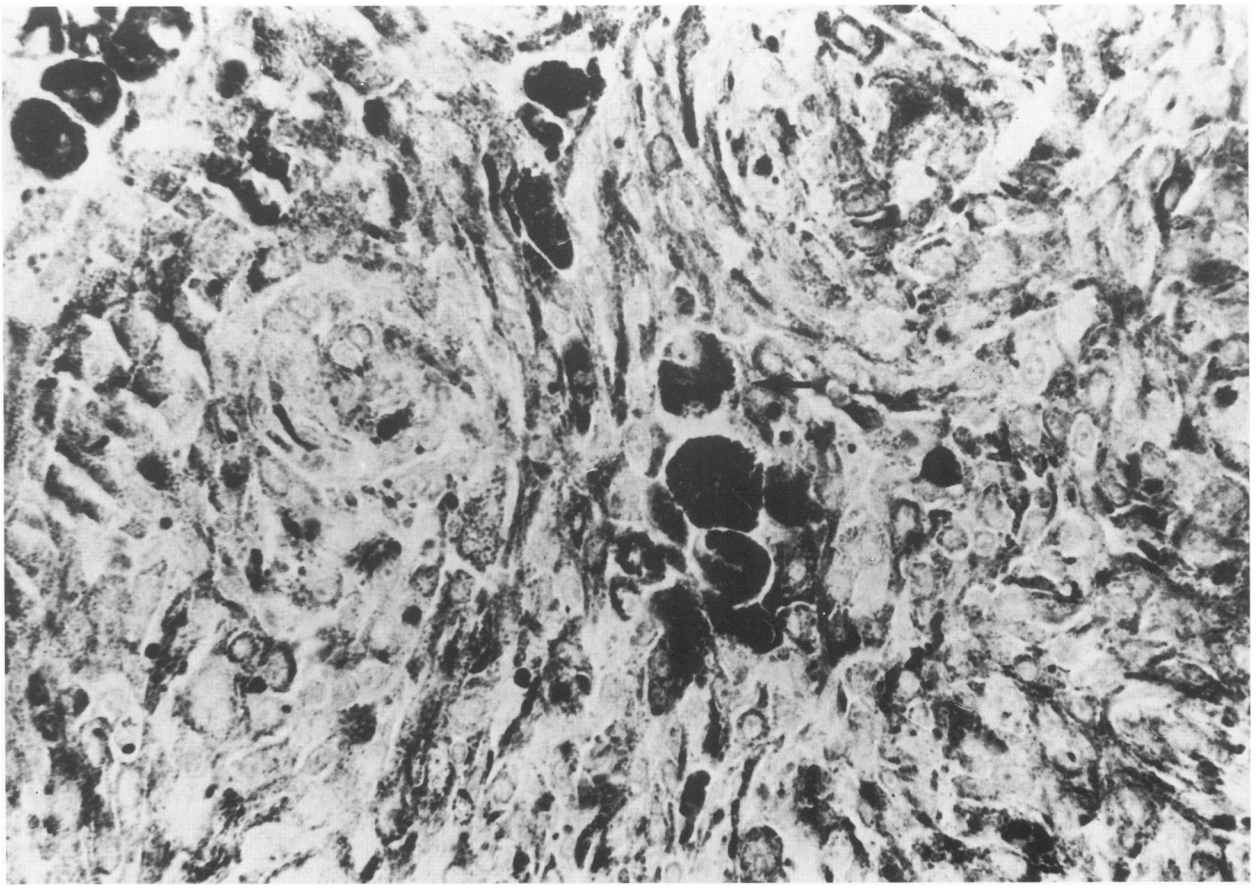

Figure 2—Invasive component showing spindle-shaped cells having heavily pigmented dendritic processes (*arrow*). Note the pigment-laden macrophages.

that occur during the spontaneous regression of melanoma lesions. As already described, Sinclair swine melanomas have a variety of histopathologic forms *in vivo*.[1] We have found that when these lesions are adapted to grow *in vitro*, the primary cultures are also morphologically variable.[7] This finding, together with the observation that several swine melanoma lesions can progress and regress simultaneously in a single pig,[3,4] suggests that tumor heterogeneity may play a significant role in the natural history of swine melanoma. Initial selection of melanoma subpopulations by short-term passage in culture and in the hamster cheek pouch[8] further confirms that different subpopulations can be isolated from the melanoma lesions by relatively simple procedures.

The Sinclair swine melanoma model enables the design of experimental protocols not easily carried out in other tumor systems. The opportunity to perform sequential biopsies on a single lesion is afforded by the large size of the swine melanomas. Similarly, the ability to perform biopsies on progressing and regressing tumors in the same animal is a unique advantage of this tumor system. This system also enables extensive sequential studies within an autologous system for studies of *in vitro* immunologic reactivity. When studies with an allogeneic system are required, the high incidence of melanomas in Sinclair swine allows the selection of melanomas from closely related swine; eg, melanomas can be selected from siblings matched for major histocompatibility antigen type. The elucidation of swine melanoma in

terms of pathologic, immunologic, and biochemical mechanisms ultimately may provide a key to the understanding and management of the neoplastic process.

Availability

Sinclair miniature swine were derived from pigs originally developed at the Hormel Institute in Minnesota. The Sinclair swine melanoma was first observed in 1967 in one animal of the Sinclair miniature swine breeding herd.[9] Experimental breeding herds of melanoma swine currently are maintained at the Sinclair Comparative Medicine Research Farm, University of Missouri, Columbia, Missouri.

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