Beyond Serendipity to an Algorithmic Approach

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Hemangiomas are heterogeneous vascular tumors (comprising endothelial cells, pericytes, myeloid cells, fibroblasts, and mast cells), have a unique natural history, and eventually involute into fibrofatty residuum (adipogenesis), which replaces the vascular tissue.[1–3] Most hemangiomas become apparent postnatally (do not proliferate *in utero*), reflective of the "maturation of the immune system in development (a layered immune system with distinct lineages [multilineage fetal and adult system] and homeostatic regulation of subsets [innate and adaptive immune traits] differentially influenced by genetic and environmental factors)".[1] In the field of tumor immunology and immunotherapy, hemangiomas of infancy can serve as a remarkable tumor model to better the understanding and range of immune responses and the mechanisms that regulate inflammatory and antitumor responses for diagnostic, prognostic, and therapeutic applications, and more specifically to serve as a model for the development of an algorithmic approach to inform on (1) clinical management, treatment strategy and (2) design, development of definitive therapies.

Currently, clinical management is limited to observation. Surgical and nonsurgical treatment modalities have mixed results (as well as potential adverse effects and/or rebound growth [incidence of rebound growth was 25.3% for aggressive tumors[2]]) with therapeutic strategies of drugs commonly used in the management of hemangiomas based on inhibition of angiogenesis (steroid therapy, interferons [IFNs], vincristine, bleomycin, propranolol, cyclophosphamide, and thalidomide[4]). We propose that the development of definitive therapies requires a robust understanding of the maturation of the host immune system in development, innate and adaptive immune systems with respect to (1) the manifestation of tumorigenesis and the environmental factors that influence immune maturation; (2) the actual mechanisms involved in potential teratogenic immunomodulation and tumorigenesis; and (3) the modulation of an inflammatory response.[5] *Environmental factors influence immune maturation* and the impact of *in utero* exposures on homeostatic regulation of immune system maturation can vary and inform on *early life exposures and potential susceptibility to disease.*

ALGORITHMIC APPROACH

We hypothesize that the vascular tumor growth curve corresponds to immune system development and the homeostatic regulation of immune system maturation, with tumor cessation corresponding to immune cell functionality and the transitions in fetal and adult immune cells (graceful transitions and an orchestrated switch; Fig. 1). Understanding the specific crosstalk between the host immune system and tumorigenesis during the stages of tumor development is important, for example, to identify the strategies tumors use to evade immunosurveillance and the therapeutic application of immunotherapy— *beyond serendipity to an algorithmic approach.*

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DISCLOSURE

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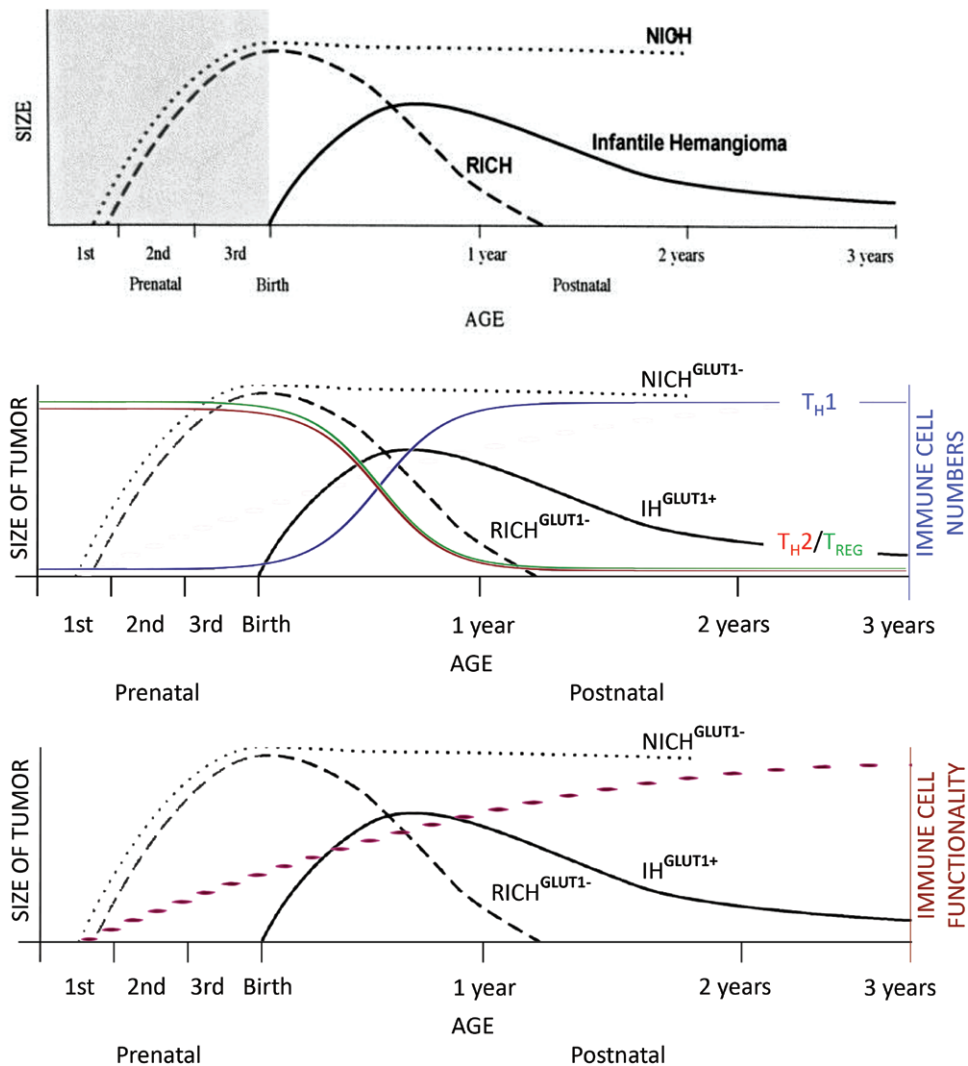
Fig. 1. Tumor growth curve, immune system development (*wishbone curve*), and ontogeny of immune response. A, Tumor growth curves (reprinted with permission from Dr. Mulliken). B, Immune system in prenatal and postnatal development—curve reflecting normal, graceful transitions in fetal and adult immune cells, and an orchestrated switch (eg, developmental switch of T helper cell [TH2] to [TH1] immunity). C, Immune system maturation and adult immune cell functionality curve. ClinicoPathological Correlation (CPC) Single-Cell Assays, Immune Signatures Panels, and Technologies for Monitoring Immune System can be developed to evaluate the impact of *in utero* exposures on homeostatic regulation of immune system maturation. Reprinted with permission from Harbi et al.[1], 2017.