Unraveling the enigma of sarcoidosis

Sarcoidosis is an uncommon, genetically-conditioned disease, affecting primarily the lungs. Most cases resolve spontaneously. It is defined by a systemic granulomatous response (SGR) of unknown cause. A granuloma is a distinctive mixed-cellular immune response that reflects failure of efficient cell-mediated processing to eliminate an immunogenic agent. An immunogen is an agent, usually a protein, capable of generating an immune response.

Sarcoidosis exhibits a number of enigmatic immunological features: To develop a diagnostic test, Kveim injected the skin of sarcoidosis subjects with a lymph node suspension from an affected subject and found that it generated GR at 28/42-days in most. The immunogenic component of Kveim suspension (KS) has defied identification, and efforts to develop a KS laboratory test to produce a cellular response have failed. Healthy individuals who fail to develop a positive tuberculin test following BCG (a non-virulent relative of the tuberculin bacillus employed to develop protective immunity) immunization are frequently KS positive, and subjects with sarcoidosis are typically tuberculin test negative. Clinical and cellular markers of severe disease are, paradoxically, associated with a favorable outcome. Suppression of the inflammatory response (to protect against fatal lung scarring), while helpful short-term, frequently proves harmful long-term by impairing resolution. Although sarcoidosis is thought to be caused by an airborne agent, in 10% the thorax is spared and the disease is confined, for example, to the heart, skin or liver.

Colin Munro developed a series of experiments using skin injection of KS to reproduce the immunological events leading to a GR. The short-term (48-hour) response was negative in normals and sarcoidosis subjects, leading to the conclusion that there was no hypersensitivity to any KS component. At 11/18-days, normals and KS-negative sarcoidosis subjects developed a dense mixed-cellular response, which included dendritic cells (these identify immunogens and convey them to the lymph nodes to generate a cell-mediated immune response). One of 13-KS positive sarcoidosis subjects developed a comparable response; 12 developed a sparse, disorganized cellular response lacking dendritic cells. Munro concluded that the granulomas characterizing sarcoidosis were a default to a primitive and less efficient response due to an inefficiency in cellular immunity. Several investigators have since confirmed dendritic cell dysfunction in persons with sarcoidosis.

The view that sarcoidosis is a syndrome (i.e., of varying cause)—not a disease—explains the failure to identify the causal agent. Inefficient cell-mediated immune response accounts for its appearance in immunologically impaired persons with defined causes such as AIDS and lymphomas. Impaired cellular immunity as its fundamental nature accounts for the lack of tuberculin test response. It accounts for failure to identify the immunogenic component of KS and an explanation for failure to reproduce the cellular features of KS response in a laboratory test. It explains the favorable outcomes associated with markers of disease severity. Most critically, it encourages a watchful approach to treatment, reserving it for individuals with critical organ—eye, brain, heart—involvement and those with definitely progressive lung disease.

Malignancies are infrequently accompanied by a SGR indistinguishable from sarcoidosis. It is likely that the SGR represents an immune response to the malignancy, not its cause, for two reasons: 1) Malignancies often generate regional granulomas, which are thought to be a response to tumor immunogens. There is no reason to think these cannot become systemic; 2) Both conditions may be evident at diagnosis. Because the inception of neither is knowable, the time course of each helps to distinguish cause from effect. Malignancies typically require years-to-decades to become evident while a SGR, as judged by the 4-6-week evolution of the Kveim test response, require a far briefer time.

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Anomalies in the dominant sarcoidosis paradigm justify its displacement.
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