Immunobiology 222 (2017) 672–675

Contents lists available at ScienceDirect

Immunobiology

journal homepage: www.elsevier.com/locate/imbio

Short communication

Anomalies in the dominant sarcoidosis paradigm justify its displacement

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ARTICLE INFO

Article history:
Received 23 September 2016
Received in revised form
27 December 2016
Accepted 27 December 2016
Available online 6 January 2017

Keywords:
Dendritic cell
Granulomatous response
Immune paradox
Immunodeficiency
Kveim
Sarcoidosis

ABSTRACT

The prevailing paradigm defines sarcoidosis as a disease of unknown etiology characterized by a systemic noncaseating epithelioid granulomatous response (SGR). This formulation fails to account for the elusiveness of the etiological agent, the nature of the Kveim response, the paradox of cutaneous delayed type hypersensitivity anergy in a setting of intense immune response and the appearance of SGR, indistinguishable from sarcoidosis, in persons with lymphohematogenous and solid neoplasms and a variety of cellular immune deficiencies. Displacing this formulation with an evidence-based alternative in which the SGR is viewed as an etiologically diverse, primitive immunological fallback due to inefficient cellular immune processing eliminates these shortcomings, providing a unifying accounting for the puzzles and violations of expectations associated with the prevailing paradigm. Its clinical import resides in the reported annual three-percent increase in sarcoidosis mortality in the past two decades (Swigris et al., 2011), which may be attributable, in part, to unneeded suppressive treatment.

Sarcoidosis is viewed as a genetically conditioned (Grunewald, 2012) disease (*i.e.*, *sui generis*) of unknown etiology. Literal observance of this definition is unworkable because, were its etiology identified, sarcoidosis would cease to exist; and it excludes any disorder of *known* etiology meeting the histopathological criteria of sarcoidosis. It thus fails to address the development of clinicopathologically indistinguishable responses in ca. 1–2% of persons with malignancies (see Appendix), histoplasmosis, tuberculosis, and beryllium exposure.

The *SGR* characterizing sarcoidosis has been considered an exaggerated immune reaction to an unknown stimulus. This formulation predicts that: (1) an immunogen, able to generate a SGR in susceptible individuals, would be identifiable by means of culture, histopathological examination, PCR amplification, serological or epidemiological evaluation, or *via* its characterization in Kveim suspension; (2) greater intensity of the immunological response, signifying disease severity, would be prognostically unfavorable; and (3) suppression of the SGR would favorably affect the outcome (see Appendix). Decades of clinical experience has supported none of these predictions. The observation that corticosteroid suppression adversely affects outcome in persons with recent onset sarcoidosis (Reich, 2003a), and that persons exhibiting the most vigorous immunological response – operationally defined by bronchoalveolar lavage (BAL) cellularity – have the most favorable prognosis challenge the view that the SGR is harmful. Ward, for example, Ward et al. (1989) found a higher percentage of lymphocytes and a higher BAL helper/suppressor lymphocyte ratio in subjects presenting with prognostically highly favorable acute onset disease (Löfgren's syndrome – bilateral hilar adenopathy, erythema nodosum, acute uveitis) *vs.* subjects with a prognostically less favorable insidious onset. Foley et al. (1989) reported that high intensity alveolitis (BAL lymphocyte percentage ≥28%) was a favorable prognostic factor for lung function in pulmonary sarcoidosis, even in patients with chronic disease. Haslam (1992) confirmed this finding, hypothesizing that, "Patients with more efficient inflammatory responses may be better able to eliminate an unknown agent or antigenic stimulus in sarcoidosis."

The inference that the putative source of the sarcoidosis immunogen is airborne, based on the observation that >90% of cases exhibit an intrathoracic component, fails to account for the bilateral symmetry and prograde progression of intrathoracic sarcoidosis (hilar adenopathy preceding pulmonary shadowing) *vs.* unilateral and retrograde progression of airborne granulomagenic agents such as histoplasmosis and tuberculosis (asymmetrical pulmonary shadowing succeeded by hilar adenopathy) or of instances of exclusively extrathoracic sarcoidosis.

A granulomatous response to an intradermal injection of a clinically validated suspension of sarcoidosis-derived splenic or lymphatic tissue is considered an immunological marker of sar-

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http://dx.doi.org/10.1016/j.imbio.2016.12.005
0171-2985/

coidosis. The unexplained features associated with this formulation are: (1) the reasons for selectivity (*i.e.*, specificity) of a "good" suspension; (2) repeated failures to develop an *in vitro* Kveim test (analogous to the beryllium lymphocyte proliferation test); (3) unsuccessful efforts to identify the immunogenic component of the suspension (Moller, 2007); (4) the declining frequency of positive responses with the duration of sarcoidosis; (5) that 0.7–2% of normals have a positive response; and (6) its frequent positivity in healthy individuals whose skin tests fail to convert following BCG immunization (Munro and Mitchell, 1987). The last implies that a positive Kveim response is a marker of cutaneous delayed type hypersensitivity (DTH) anergy.

The SGR has been conceived of as an exaggerated immune reaction. The paradoxical development of a SGR in immunologically compromised persons – *e.g.*, those with AIDs during immunological reconstitution and its extraordinarily high incidence among individuals with combined variable immunodeficiency disease – violates expectation as does the development of sarcoidosis in some recipients of TNF-α inhibitors. Furthermore, the prevailing model fails to account for both the "immune paradox" of sarcoidosis, DTH anergy in a setting of exuberant systemic granulomatous response, and for the protective effect of cigarette smoking.

Kuhn described the conditions required for fundamental changes in natural science in *The Structure of Scientific Revolutions* (Kuhn,1996), grounding his reasoning on historical observations drawn largely from physics (Newton *vs.* Einstein), chemistry (Priestly *vs.* Lavoisier) and astronomy (Ptolemy *vs.* Copernicus). He found that a paradigm crisis arose when data from nature failed to conform with the dominant epistemology, and when anomalies and violations of paradigm-induced expectations were experienced. He observed that cumulative examples subverting the tradition of scientific practice led to the sense that something was fundamentally wrong. Kuhn emphasized that the revolution in scientific thought was not cumulative, but invariably transformative; *i.e.*, the supplanting paradigm did not augment; it displaced the previous theory. He likened Its effect to a gestalt-like transformation *e.g.*, the image-ground reversal in the rabbit-ears/duck-beak exemplar. He further pointed out that theory choice depended not on demonstrable "truth," a philosophically elusive objective, but on practical, empirical criteria: (1) which theory better fit the facts, served to explain the evidence at hand; (2) its comparative simplicity, *e.g.*, Copernicus (*De revolutionibus orbium coelestium*) *vs.* Ptolemaeus (*Almagest*; <Gk, *al magiste*, the greatest); (3) its promise as a guide to future research (fruitfulness); (4) its ability to resolve some outstanding problem not otherwise resolvable; and (5) its preservation of a large part of previously accrued problem solving ability. Accuracy, predictive ability, self-consistency, plausibility, and compatibility with other theories were additional desirable paradigm values. He found the demonstrated ability to set up and to solve puzzles presented by nature to be the dominant criterion for theory-choice.

An alternative sarcoidosis paradigm can be constructed by combining the concepts advanced by Scadding and Mitchell (1985) with the experimentally-derived, pathophysiological mechanism proposed by Munro (see below). Scadding and Mitchell rejected the description of sarcoidosis adopted at the Seventh International Conference on Sarcoidosis in 1975 – "Sarcoidosis is a multisystem granulomatous disorder of unknown etiology, most commonly affecting young adults and presenting most frequently with bilateral hilar adenopathy. ." – on grounds that the lengthy "... description was intended to stand in place as a definition;" "... that it provided no way in which agreement might be reached in a case in which informed observers disagree; and that it lacked a proviso that changes of a specific type must be widely disseminated." They recommended its replacement with a morbid anatomical definition: "Sarcoidosis is a disease characterized by the formation in all of several affected organs or tissues of epithelioid-cell tubercles, without caseation though fibrinoid necrosis may be present at the centres of a few, proceeding either to resolution or to conversion into hyaline fibrous tissue." They added: "Since there is no agreement concerning the aetiology of sarcoidosis, nor indeed whether sarcoidosis is an aetiologically homogeneous group, no reference to aetiology can be made in the definition." This definition serves to exclude from consideration, *a priori,* plausible etiological candidates – cancer, histoplasmosis, tuberculosis, beryllium – (Reich, 2012).

Scadding and Mitchell point out an additional benefit of excluding the requirement of unknown etiology from the definition (Scadding and Mitchell, 1985):

"... sarcoidosis may represent an unusual reaction to an agent or agents already known and normally causing a well-recognized disease, but difficult to demonstrate in the unusual manifestation of sarcoidosis." The report of a patient with progressive systemic histoplasmosis succeeded shortly thereafter by apodictic, rapidly progressive, stage IV sarcoidosis requiring corticosteroid therapy supports this hypothesis. Culture, tissue biopsy and serology during the latter episode excluded persistent infection with histoplasmosis (Reich, 2003b). The definition proposed by Scadding and Mitchell eliminates the anomaly of persistent failure to ascertain *the* etiology of sarcoidosis: Like the unsuccessful 19th century searches for the notional entities, *aether, caloric,* and *phlogiston*, efforts to identify *the* etiology are futile because it does not exist.

Munro et al. (1986a) employed the Kveim test as an experimental model of sarcoidosis to replicate and thus identify the immunohistochemically defined cellular immunological events leading to a positive response in Kveim subjects *vs.* normals. A positive test, biopsy-assessed at 28- to 42-days, is compositionally identical to a sarcoid granuloma (Moller, 2007). Positivity has been assumed to reflect hypersensitivity to some component of the suspension, although no such component has been identified. Initially, the authors investigated the 48-h response to intradermal injections of 10-units of tuberculin and of validated Kveim suspension (Munro et al., 1986a). Positive tuberculin responses, signifying intact DTH, were characterized by dense, dermal, lymphocytic infiltration. Kveim suspension failed to elicit this response in both normals and Kveim-positive sarcoidosis patients; their cellular components were indistinguishable. The investigators concluded that there was no evidence of hypersensitivity to any component of the Kveim suspension.

Next, to understand the genesis of the granulomatous response, the authors compared the 11- and 18-day (*i.e.*, initial) response to Kveim suspension in healthy controls, Kveim-negative, and Kveim-positive sarcoidosis subjects (Munro et al., 1986b). The majority of healthy controls and Kveim-negative sarcoidosis patients responded with features characteristic of DTH reactions: a dense perivascular infiltrate of mononuclear cells composed of T-cells of helper and suppresser types, with markers of activation (Tac+; Leu9+), and dendritic Langerhans cells (OKT6+; RFD1+) with strong HLA-DR expression. Only 1 of 13 Kveim-positive sarcoidosis patients developed a comparable response. The remaining 12 developed a more gradual response characterized by close associations of phagocytic macrophages and helper T-cells, some of which were also Tac+; dendritic Langerhans cells were absent. The authors inferred that the SGR characterizing sarcoidosis represented a default to an immunologically more primitive and less efficient response as a consequence of an undefined inefficiency in cell mediated immunity. In this formulation, DTH anergy and exuberant SGR – the "immune paradox" of sarcoidosis – were dual manifestations of the same inefficiency. The observation that a high proportion of healthy, young, British adults who failed to convert their tuberculin test following repeated BCG immunizations proved