PTX3 in Granuloma Formation and Sarcoidosis: Helping Macrophages Accept a "Complement"

Sarcoidosis is a multisystem disease characterized by the accumulation of noncaseating granulomas in affected organs (1, 2). It is proposed to originate from a prolonged or dysregulated immune response to as yet undefined antigen(s) in genetically susceptible individuals (3). The prognosis is highly variable, ranging from spontaneous remission to severe phenotypes that respond poorly to immunosuppression and constitute a substantial proportion of disease-related hospitalizations and deaths (2). Because better understanding of the molecular mechanisms accounting for this heterogeneity might be leveraged for clinical benefit, the execution of high-quality studies of granuloma formation in sarcoidosis remains a critical unmet need.

The nonnecrotizing granulomas seen in sarcoidosis contain tightly packed collections of macrophages, epithelioid cells, multinucleated giant cells, and $CD4^+$ (cluster of differentiation 4) T lymphocytes. Although decades of work has linked the latter population to disease, far less is known about the contribution of other immune cells in this context. Unlike lymphocyte-driven adaptive immune responses, which are mediated by highly specific receptor–ligand interactions, innate immune responses are initiated by pattern recognition receptors that recognize the physical or chemical ligand features of their target. One pattern recognition receptor class is the PTX (pentraxin) superfamily, a group of fluid-phase humoral pattern recognition molecules (4) that is composed of several subclasses. Within this superfamily is PTX3 (pentraxin 3), a proinflammatory molecule whose manifold properties include macrophage activation (5, 6) and complement-dependent inflammatory (7, 8) and remodeling (9) functions. Interestingly, despite previous work describing PTX3 (10) or complement anomalies (11, 12) in sarcoidosis, until recently the evidence connecting these entities has been scant.

In this issue of the *Journal*, Gonçales and colleagues (pp. 1140–1152) present a novel molecular link among PTX3 deficiency, amplified complement activation, and granuloma formation in experimental models and in patients with sarcoidosis (13). By combining animal studies, cell culture work, and primary human biospecimens, the authors demonstrate that PTX3-deficient mice are prone to exacerbation of the mycobacterium superoxide dismutase A mouse granuloma model in a manner that is rescued by PTX3 administration; that PTX3-deficient macrophages are susceptible to C5a (complement component 5a)–mediated activation of the metabolic checkpoint kinase mTORC1 (mammalian target of rapamycin complex 1) and its associated endpoints of glycolytic reprogramming, proliferation, and aggregation; that genetic variation in the human gene PTX3 augments *ex vivo* granuloma-like structure formation; and that circulating PTX3 concentrations are associated with disease persistence in patients with sarcoidosis. When viewed in combination, these findings suggest a paradigm in which a paucity of PTX3 fosters an environment in which complement-induced macrophage activation favors the formation of granulomas, or granuloma-like structures, in several modeling systems and that this axis appears to be at least partially active in patients with sarcoidosis.

These compelling observations provide new information regarding the mechanism(s) through which macrophages participate in granuloma formation and relate this discovery to the clinical features and outcomes of patients with sarcoidosis. The work presents a rigorous cross-platform approach that uses logical and well-designed *in vivo* and *in vitro* experimental system, novel PTX3-deficient mice, stringent gain- or loss-of-function strategies, and the elegant use of biospecimens from two independent sarcoidosis cohorts. It should be noted that progress in this disease has been stymied by the lack of a consensus modeling system. Acknowledging this shortcoming, the authors are to be applauded for their parallel studies of granulomatous inflammation in mice, the formation of granuloma-like structures *ex vivo*, and clinical phenotypes in humans. Hence, it is easy to predict that future studies of PTX3 and complement will enhance the understanding of sarcoidosis and perhaps one day inspire novel therapies replicating the successful development of a related protein, PTX2 (pentraxin 2), for fibrotic conditions affecting the lung (14) and other organs.

The work's relatively few shortcomings provide ample opportunity for future study. For example, the authors are unable to definitely identify PTX3's source, though the preponderance of evidence suggests at least partial contribution of macrophages. This question could be addressed by the generation of transgenic mouse lines targeting PTX3 deletion to macrophages under inducible and specific promoters. It is unknown whether the interaction between PTX3-deficient macrophages and complement components stimulates granuloma formation via direct or indirect mechanisms, a question that could be answered with labeling methods of lineage tracing. It is also not clear whether the benefit of exogenous PTX3 administration is preventive or therapeutic, and the question could be addressed with more detailed kinetic studies and treatment schedules. Finally, better understanding of relationship among genotype, tissue and circulating PTX3 concentrations, and sarcoidosis phenotype will be required to elucidate what connection, if any, exists between PTX3 and persistent disease.

In conclusion, the study of Gonçales and colleagues (13) convincingly depicts the relationship among PTX3, complement activation, and macrophages. Its significance extends beyond this relatively well circumscribed molecular observation to represent a conceptual advance uniting innate immunity, humoral factors,

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granuloma formation, and sarcoidosis that "complements" the proposed immunopathogenic paradigm of this enigmatic disease. ■

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Household Air Pollution, Passive Smoking, and Lung Cancer
Do We Know Enough about This Conundrum?

The Global Burden of Disease (GBD) collaboration reported 2.2 million incident cases of lung cancer in 2017, a 37% increase from 2007 globally in 195 countries; a total of 1.9 million deaths; and 40.9 million disability-adjusted life-years in both sexes, although this was higher in males than in females (1). The lung cancer cases increased by 17% from 2007 to 2017 in high–sociodemographic index (high-SDI) countries, 62% in middle-SDI countries, and 49% in low-SDI countries, with a change in age structure, population growth, and age group being the primary factors for the increase (2). Several studies, including a study by Sir Richard Doll on British doctors published in 1976 (3), emphasize smoking as a primary driver of lung cancer incidence, with GBD studies reporting the relative risk of lung cancer from tobacco smoke being 3.4 at 10 pack-years and 6.5 at 20 pack-years (2). The attributable fraction of lung cancer mortality due to smoking (males, 75.4%; females, 36.6%) has been higher in males because of higher smoking prevalence than in women (1).

Ambient air pollution (AAP) (4) has been the other leading risk factor for lung cancer mortality. Other contributors to lung cancer include exposure to household air pollution (HAP); secondhand cigarette smoke (SHS); and occupational exposure to asbestos, nickel, chromium, arsenic, and radiation (5). Although many studies from high-income countries have reported that exposure to AAP and smoking is causally associated with an increase in mortality of cardiorespiratory diseases (6) and lung cancer, there is a lack of prospective evidence from low- and middle-income countries (LMICs), where HAP from burning solid fuel for domestic cooking and heating purposes in addition to AAP in cities is an area of significant health concern (7). In certain LMICs, up to 50% of the AAP is contributed by HAP from solid fuel burning and 30% from fossil fuel burning, of which 50% comes from coal burning (8). Globally, there has been a decline in the use of solid fuels for cooking from 53% (45–60%) in 1990 to 36% (30–43%) in 2020, and if the current trends continue, use will be about 31% in 2030; however, the total number of the population cooking with solid fuels was 2.8

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