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A Ginger Root or Plum Model for the Tuberculosis “Granuloma”?

Many tuberculosis (TB) researchers tend to view lung lesions as largely spherical “granulomas” and cavities as granulomas that have become necrotic, expand, and erode into bronchi. Clinical TB pathologists and radiologists, on the other hand, are aware that this image is an oversimplification, partially induced by the shift from human autopsies to animal models for immunopathology studies. Pioneering clinical histopathology studies from the preantibiotic era showed that postprimary disease begins as infection of lipid-laden foamy alveolar macrophages and bronchioalveolar obstruction progressing to caseating cavitary disease. Dissemination primarily happens via bronchogenic spread of both primary and post-primary TB but may fail to characterise both primary and post-primary TB but may fail to

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coordinate and align them as humans do (14). Other animal model features are reminiscent of the human findings described here but may not have been correctly interpreted in the absence of high-resolution 3D imaging methods. The study by Wells and colleagues (10) constitutes an opportunity to pursue formal CT studies in animal models, to determine the extent of bronchogenic spread and bronchial wall necrosis, to establish their contribution to disease dissemination in each model, and to discover how models can be manipulated to better recapitulate selected aspects of human TB. For example, rapid-onset exudative lesions leading to cavities from dissolution of caseous pneumonia can be reproduced in rabbits by prior sensitization or immunization (15).

How do those findings impact the pharmacology of TB drugs? Despite our oversimplified view of granuloma progression (16), drug partitioning at the caseum–cellular interface remains a sound concept, but a purely lesion-centric model omits one important compartment: the lumen of airways where a mix of intracellular and extracellular bacilli is found in mobile necrotic material during bronchogenic spread. Importantly, these bacterial populations likely transit in and out of microenvironments that are nonpermissive to replication along the bronchial tree. This suggests that temporal and spatial microenvironment dynamics contribute to differential drug susceptibility, which should be taken into consideration when designing drug regimens. In addition, genetically resistant bacteria may not be as contained within individual cavities as previously thought.

Complex networks of connected lesions also make the case for inhalation drug delivery, at least in patients with extensive cavitary disease who require longer treatment duration to achieve cure (17). Given the radiological and pathological similarities between TB and nontuberculous mycobacterial (NTM) lung disease, this work provides an incentive to consider CT studies in patients with NTM, as lung resection surgery is a therapeutic option for drug refractory cases. Administration of amikacin—a pillar of NTM disease therapy—by inhalation has become more widespread in clinical practice. Whether this comes with a therapeutic benefit and what the underlying mechanisms are remain to be formally established.

Concepts are the drivers of research. Using an elegant suite of multimodal imaging, Wells and colleagues (10) leverage the power of 3D μCT to reveal unprecedented high-resolution structures of human TB lesions and generate awareness that TB “granulomas” are more connected and complex than generally appreciated. The coordinated study of human TB pathology and disease progression in animal models, using a panel of CT-derived modern technologies, could help manipulate these models to address long-standing questions more adequately about host–pathogen relationships and the development of targeted therapeutics and vaccines.

Figure 1. Tuberculosis lesions are connected. (1) One form of postprimary tuberculosis disease begins as lipid or lipoid pneumonia, with bacillus-laden foamy alveolar macrophages and neutrophils. (2) Bronchiolar obstruction and microvascular occlusion associated with delayed-type hypersensitivity leads to the formation of small caseating cavitary foci. (3) Dissemination primarily happens via bronchogenic spread. (4) Nodules grow along the bronchial tree and airways get progressively replaced by connected lesions oriented along the bronchial and vascular network, as visualized by the study of Wells and colleagues. DTH = delayed-type hypersensitivity. Illustration by Jill Gregory.

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