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Mathematical and computational approaches in understanding the immunobiology of granulomatous diseases

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Abstract

A granuloma is a physical pathological structure that manifests when the host mounts an immune response to fend off pathogens/infections, immunological aberrations, irritants, inflammations and other foreign particles. It is an amalgamation of immune cells (lymphocytes, phagocytes (mostly macrophages and their derivatives) plasma cells, neutrophils and eosinophils), pathogens or foreign particles or irritants, fibroblasts, epithelioid cells and multi-nucleated giant cells. This well-organized dynamic structure form after an ingested pathogen or particle finds its way into tissues. The host will then mount a response to prevent the pathogen from replicating or the foreign particle from propagating inflammation. Multiple granulomas can form upon infection/invasion in a single host. The ensemble of these structures dictates the state of disease manifestation and end points, such as rapid, fulminant infections, chronic persistent states (both symptomatic and asymptomatic) or sterilization where the infection gets cleared and cure is established. Studying granuloma formation and how it shapes immune responses is an enigma, mainly because they develop at remote locations, which makes the acquisition of relevant biological readouts a nightmare. Therefore, researchers are resorting to the use of computational inference techniques as a gateway to gain more insights. Mathematical and computational modeling approaches have been used to elucidate the mechanisms driving granuloma formation, function of granulomas, and disease progression in these granulomatous diseases. However, the use of mathematical modeling to elaborately explain non-tuberculosis infections is still primal. The goals of this review are i) to review existing modeling studies describing the initiation, progression and development of different granulomatous diseases, and ii) to suggest how existing modeling approaches can be exploited to understand the immunobiology of granulomatous non-TB infections.

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The biology of granuloma formation

There are diverse causative agents that lead to granuloma formation. They can be summarized into 4 groups (1) T cell-mediated immune granulomas (pathogens and infections), (2) with unknown etiology, but with a T lymphocyte mediated profile, (3) foreign body induced granulomas (4) malignant tumor based granulomas (see Table 1) [1–7]. The infecting pathogen, foreign bodies or irritants invoke tissue inflammation, creating a wave of danger signals with a cytokine and chemokine gradient that leads to the influx of several immune cells to wall off the intruder [4,8–12]. In infections, pathogens elicit the inflammations and immune priming along different pathways (see Figure 1 for a general diagram), then the granuloma forms to prevent infection dissemination [7,9,13–20]. The pathogen is contained within the granuloma, however, some pathogens can evade killing and continue replicating within the granuloma [21–23]. As a result, the granuloma structure becomes a haven for continued bacteria replication and persistence, mostly because immune effectors and antimicrobial agents poorly access it [23,24]. Failure to contain the pathogen will result in granuloma expansion, which can slowly evolve into a cavity. Cavitation is a presentation of a granuloma gone rogue and is evidence for a failed immune system, especially in lung mycobacteria infections such as *Mycobacterium tuberculosis* (MTB) and *Mycobacterium avium* complex (MAC) infections [21,24–27].

A major challenge in studying the host immune responses in granulomatous infections is that they typically form in remote locations, therefore making it difficult to obtain experimental data to fully characterize the disease. In infections such as MTB, MAC, *M. Kansasii*, and Leprosy, the granuloma structure and its function is central to understanding infection progression in immune competent and non-competent hosts [2,16,21,23,28]. Also non-mycobacterial infections such as Sarcoidosis, Leishmania, Schistosomiasis and several tumors [1,3,5,29–32] are presented with granulomas.

Table 1

Classification of granulomatous diseases and disorders. Agent vs cause and site of granuloma.

Generic cause	Causing agent	Nature of granuloma	Location/site of formation	Modeling studies	Experimental model
Bacteria	1) *Brucella* spp. 2) *Yersinia* 3) *S. aureus*	Necrotizing	1) Skin 2) Skin 3) Skin	1) NA 2) NA 3) NA	1) In-vitro, Mouse, pigs, NHP 2) In-vitro, Mouse, Rodents 3) In vitro, *C. elegans*, Mouse
Mycobacteria	1) MTB 2) *M. leprae* 3) *M. Kansasii* 4) MAC	Necrotizing	1) Lung 2) Skin 3) Lung 4) Lung	1) [82] 2) NA 3) NA	1) In-vitro, Mouse, Rabbit, NHP 2–4) In-vitro, Zebrafish, Mouse
Fungi	1) *Candida* sp. 2) *Aspergillus fumigatus* 3) *Coccidioides* spp.	Non-necrotizing -Necrotizing Non necrotic	1) Liver 2) Lung/skin 3) Lung, skin, kidney, liver	1) NA 2) NA 3) NA 4) NA	1) In-vitro, Mouse, *C. elegans*, Drosophila 3) In-vitro, Mouse, Rabbits, NHP
Protozoa/parasitic	1) *Leishmani* 2) *Toxoplasma gondii* 3) *Schistosoma* sp.	Necrotizing	1) Liver, skin 2) Lung/lymph node, liver 3) Liver	1) [19,83–86] 2) NA 3) NA	1) In-vitro, Birds, Mouse 2) In-vitro, Mouse, Guinea-pig, Cats 3) In-vitro, Rodents, NHP
Immune disorders	1) Sarcoidosis 2) Crohns 3) Churg-strauss	Non-necrotic	1) Lung, skin, liver 2) Gut, kidney, liver 3) Lung, skin, lymph node	1) [87] 2) NA 3) NA	1–3) In-vitro, Mouse

The formation of granulomas in these diseases is concomitant with the expressed immune responses. As illustrated in Figure 1, in immune-competent individuals granuloma formation gravitates toward infection containment and control (Figure 1A). In this case granuloma formation is a hallmark of an effective immune response. However, in non immune-competent individuals, granuloma formation fails to contain or resolve the infection. In these scenarios, the Th1/Th2 balance plays an important role in disease pathology and granuloma formation, Figure 1B. Intracellular infections are normally characterized by an initial Th1 immune response [33] that hands over to a Th2 response with infection progression. The switch in Th1/Th2 dominance leads to poor disease containment and fibrosis (the Th2 response stimulates fibroblasts) at the disease chronic stage, Figure 1B. Apart from the autoimmune related diseases, a classical example of a Th2 granuloma is observed in Schistosomiasis infection. Therefore, without understanding how the granuloma molds the immune systems or how the immune responses interact with foreign particles or irritants to forge the formation of granulomas, we are left with a partial immune picture we can hardly explain. Our failure to clearly decipher host immune responses underlying these diseases and pathologies is the reason behind slow or no discovery of reliable therapeutic regimens, biomarkers of protection and infection progression, as well as in some cases biomarkers of treatment outcomes [34,35]. This has led to experimental studies and clinical trials rife with products that are suboptimal, underperforming, cannot meet the expected outcomes and that are also accompanied by several contra-indications [36–39].

Several studies have shown that granuloma structures can be exploited by infectious pathogens and therefore can be sanctuaries that protect pathogens from drugs and immune responses [24,40,41]. In such cases, granulomas become hot spots where bacterial replication, resistance and persistence are fostered. However, on the other hand, a robust stratum of granulomas plays a critical role in curbing disease/infection dissemination, hence protecting the host from inflammation and tissue erosion [16,42].

Investigating the possible interplay between microbial communities and the host when facing threats by "non-self" pathogens can represent another avenue of research in dissecting the causes of granulomatous diseases. Host-pathogen interaction studies usually consider a one-to-one relationship between the host immune system and a single pathogen. However, the tropism of most granulomatous infections is in locations within the host that are crowded by millions of different bacterial species (microbiome). Different microbial communities emerge in different sites/organs, potentially driving the evolution and stability of these host-microbial networks in disproportional ways, therefore driving intra-individual and inter-individual heterogeneous immune responses. Recent studies have unveiled the association between specific microbial communities and either susceptibility or resistance to infections (for example in *Clostridium difficile* infection [43–45]). Furthermore, other studies used these association studies to explore potential treatment options based on manipulating these microbial communities [46,47]. The mechanisms by which these treatments were eventually