Rabbit Nocardiosis as a Tuberculosis Mimic: Immunopathology and Translational Gaps : A Narrative Review

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Abstract

Nocardia spp. are opportunistic, granuloma-forming bacteria whose pulmonary disease can closely mimic tuberculosis (TB), complicating diagnosis and management. Rabbits—capable of developing human-like, organized granulomas with variable necrosis—offer a promising bridge between small-rodent models and human disease. This narrative review synthesizes evidence on the immunopathology of *Nocardia* infection in rabbits, maps points of convergence and divergence with human TB immunology, and highlights critical translational gaps. We examined studies of granuloma architecture, cell-mediated and humoral responses, intracellular survival strategies, and host susceptibility, integrating comparative data from human, rabbit, and rodent work to clarify mechanism and relevance. Overall, rabbits mount robust T-cell–dependent responses and can contain infection within structured granulomas, yet susceptibility varies with inoculum and immune status. Evidence for antibody contributions remains sparse and sometimes conflicting, and host genetic determinants in rabbits are poorly defined relative to known human risk pathways. Targeted studies dissecting B-cell functions, antibody isotypes, and genetic drivers in rabbit nocardiosis are needed to strengthen the model's translational value for both nocardiosis and TB, and to inform future immunotherapeutic or vaccine strategies.

Keywords: Nocardia ; Tuberculosis ; Rabbit model ; Granuloma ; Cell-mediated immunity ; Humoral immunity ; Host susceptibility

Introduction

Tuberculosis (TB), caused by *Mycobacterium tubercul**133*** | *P a g e osis*, is characterized by chronic granulomatous inflammation and remains a leading cause of infectious mortality worldwide. *Nocardia* are aerobic actinomycete bacteria that can cause nocardiosis – an opportunistic infection often affecting the lungs, skin, or brain. Clinically, pulmonary nocardiosis can closely resemble TB in terms of symptoms and radiologic appearance, including cough, cavitary lung lesions, and chronic course[1]. Both *Nocardia* and *M. tuberculosis* are partially acid-fast intracellular pathogens that elicit granuloma formation as a host defense mechanism. Given these similarities, *Nocardia* infections in animal models are of interest for understanding

TB immunopathology. Animal models are indispensable for studying TB immunity; however, each model has its limitations. Mice, the most common model, develop granulomas that are less organized and lack the caseous necrosis typical of human TB[2], [3] . Guinea pigs are highly susceptible to *M. tuberculosis* and develop necrotic granulomas; however, they cannot control the infection and usually succumb, precluding long-term studies. Rabbits occupy an intermediate position; they mount a moderate cell-mediated immune response (delayed-type hypersensitivity) and form organized, caseating granulomas, and some rabbit strains can even control *M. tuberculosis* infection, modeling latent TB infection. Notably, rabbits (including available inbred strains) are relatively resistant to *M. tuberculosis* and often require inhalation of hundreds of bacilli to establish an infection[4], [5]. This relative resistance can mirror the human spectrum, where many exposed individuals are infected or clear the disease without symptoms. Thus, rabbit models offer the potential to study both active and latent TB within a single species.

Rabbits are less frequently used in the context of *Nocardia*. Early 20th-century attempts to induce nocardiosis in laboratory animals yielded conflicting results, with some investigators reporting rapid death of rabbits from *Nocardia asteroides* infection and others observing minimal illness[6], [7]. These inconsistencies were later attributed to differences in the inoculum preparation and strain virulence. Subsequent studies showed that *Nocardia* could infect mice, guinea pigs, and rabbits when proper techniques (e.g., using adjuvants like gastric mucin or standardized bacterial phase of growth) were applied. Rabbits, like humans, tend to restrain *Nocardia* infections unless high doses or immunosuppressive conditions are present. For example, in an ocular nocardiosis model, normal rabbits cleared a low-dose intraocular *Nocardia* infection with only transient lesions, whereas immunosuppressed rabbits developed progressive ocular disease resembling that of immunocompromised patients. This suggests that robust innate and adaptive immunity in healthy rabbits can often contain *Nocardia*.[8], [9], [10]

Given their unique immune response, rabbits could serve as a useful model to dissect host defenses against *Nocardia* and draw parallels with human TB. *Nocardia* spp. are facultative intracellular pathogens that survive within macrophages and induce granulomatous inflammation, similar to *M. tuberculosis*. However, there are significant gaps in our knowledge regarding the specific immune response of rabbits to *Nocardia*. Most immunological insights into nocardiosis come from mouse models or in vitro studies, which have limitations in mimicking human pathology[11], [12]. This review aims to critically examine the current knowledge of immunity to *Nocardia* in rabbits, compare it to what is known in human TB, and highlight open questions. In doing so, we hope to clarify the translational value of rabbit models and identify areas where further research is needed to improve our understanding of both nocardiosis and tuberculosis.

Granuloma Formation in Rabbits versus Other Models

Granulomas are the hallmark of both nocardiosis and tuberculosis, serving as structured immune aggregates that attempt to contain the infection. In rabbits infected with *M. tuberculosis*, granulomas in the lungs are typically well-organized, consisting of a central core of infected macrophages (sometimes undergoing epithelioid transformation) and multinucleated giant cells, surrounded by a cuff of lymphocytes. Depending on the strain of *M. tuberculosis* and dose, rabbit granulomas can exhibit caseous necrosis at the center, and in certain models, progression to

liquefaction and cavitation has been observed – features closely mirroring human pulmonary TB lesions[13], [14]. For instance, infection of rabbits with a high-dose virulent *M. tuberculosis* (e.g. HN878 strain) or prolonged infection can lead to chronic cavitary tuberculosis, whereas lower doses of a milder strain (e.g. CDC1551) may result in sterilization of infection without necrosis. This spectrum—ranging from contained, non-necrotizing granulomas to destructive necrotizing ones—demonstrates rabbits' utility in modeling both latent and active TB.[15]

Nocardia infections also induce granulomatous inflammation. In humans, pulmonary nocardiosis often presents as chronic suppurative disease with granuloma formation and localized pneumonia or abscesses. However, establishing an animal model for pulmonary nocardiosis proved challenging. Mice can clear *Nocardia asteroides* lung infections within a week under normal conditions, indicating that small rodents rapidly mobilize effective immunity (e.g. neutrophils and Th17 cells) to prevent granuloma maturation[16]. In contrast, granulomas were observed in mice only when extremely high inocula of *Nocardia* were used or when microcolony clumps of bacteria were introduced intranasally. For example, BALB/c mice given 10^8 colony-forming units (CFU) of *N. brasiliensis* intranasally developed discrete pulmonary granulomas by 3 weeks post-infection, whereas 10^9 CFU caused acute fatal disease and 10^6 CFU caused no lesions[17] . These granulomas contained clusters of *Nocardia* at their cores (detected by acid-fast staining), surrounded by activated macrophages and lymphocytes. Over time, especially with lower-dose infections that allowed survival, the lesions in mice could progress to large abscesses with extensive necrosis by six months[18], suggesting that persistent *Nocardia* infection can eventually overwhelm host control and destroy lung tissue.

In rabbits, very few in vivo studies have documented granuloma formation due to *Nocardia*. Pioneering work by Beaman and colleagues in the 1970s–1980s demonstrated that rabbit alveolar macrophages can be infected with *Nocardia* in vitro, and that these macrophages exhibit an innate capacity to limit *Nocardia* growth. However, attempts to create a pulmonary nocardiosis model in rabbits were limited. One study noted that even though rabbit lung macrophages could be infected in culture, live rabbits experimentally given *Nocardia* did not develop clear lung disease in those trials[19], [20]. It is likely that, akin to the mouse, an extremely high infectious dose or an immune-compromised state is required for rabbits to develop disseminated nocardial granulomas. One historical report by J. Bullock (1983) described an intraocular *Nocardia* infection model in rabbits: inoculation of ~10^3 *Nocardia* CFU into the retinal artery led to localized granulomatous lesions in the eye which were self-limited in immunocompetent rabbits, but became destructive when rabbits were treated with corticosteroids. This indicates rabbits can form granulomas in response to *Nocardia* locally, but systemic infection may be rapidly controlled. Overall, the literature suggests that rabbit tissues are capable of granulomatous inflammation with *Nocardia*, but standard pulmonary models have not been established [20], [21].

Importantly, granulomas in rabbits and humans share another key feature like hypoxia Figure 1 . Studies using hypoxia markers have shown that caseous TB granulomas in rabbits (and guinea pigs) develop hypoxic cores similar to human lesions . This microenvironment impacts immune cell function and antibiotic efficacy. Whether nocardial granulomas in rabbits (if generated) would similarly develop necrotic, hypoxic centers is unknown, but chronic mouse lesions do show extensive necrosis[22] , implying that *Nocardia* can drive such pathology given prolonged

infection. The propensity for rabbits to resolve infection before necrosis appears (as seen with TB CDC1551 strain) versus progress to necrosis (with more virulent strains or immune suppression) underscores that necrosis is not an inevitable outcome but rather a consequence of an overwhelmed immune response[23], [24]. In summary, rabbit models demonstrate that granuloma formation per se is a conserved response to both *Nocardia* and *M. tuberculosis*, but the extent of necrosis and maintenance of granuloma integrity depend on the balance between pathogen virulence and host immune efficacy. Rabbits' ability to tip that balance towards containment (often avoiding necrosis) is a notable difference from more susceptible species.

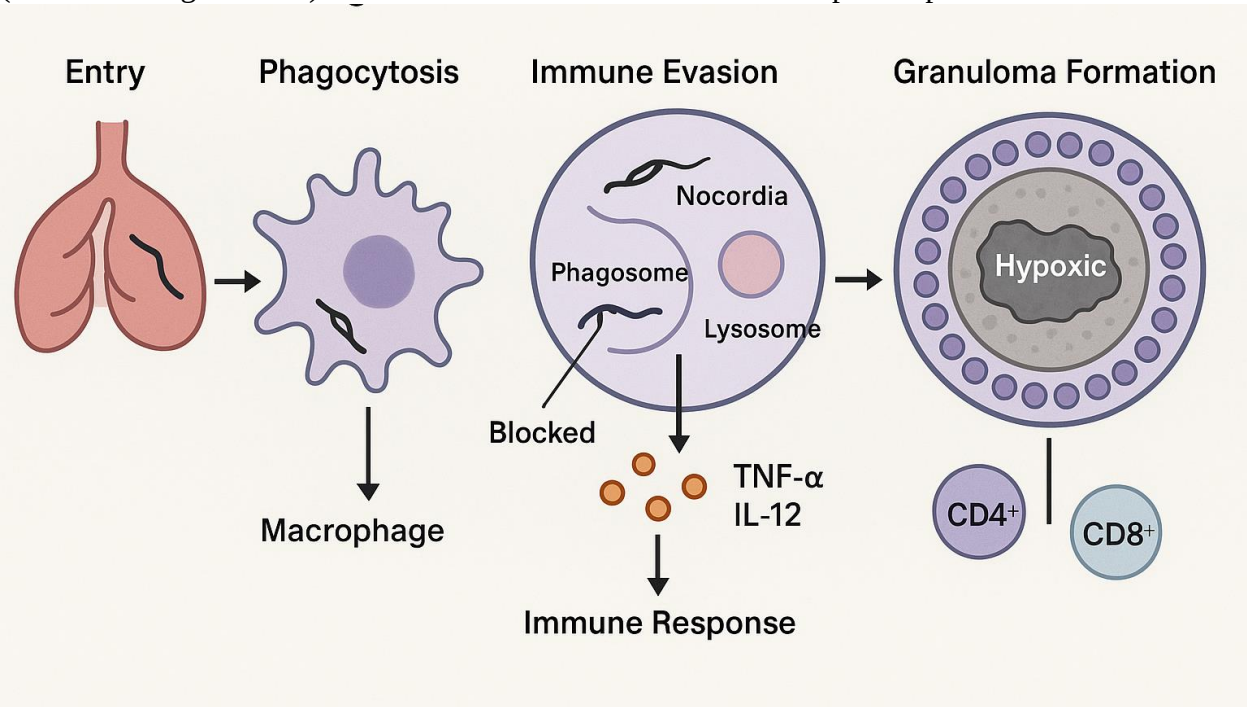

Figure 1. Conceptual model of pulmonary Nocardia pathogenesis and TB-like granuloma formation. After inhalational entry, bacilli are phagocytosed by alveolar macrophages but persist intracellularly by blocking phagosome–lysosome fusion. The ensuing cytokine milieu (notably TNF-α and IL-12) recruits and activates T cells, driving formation of organized granulomas with a hypoxic core. $CD4^+$ T cells orchestrate macrophage activation, while $CD8^+$ T cells contribute cytotoxic containment

Cell-Mediated Immunity: T Cells, Macrophages, and Cytokines

Effective control of *Nocardia* and *M. tuberculosis* largely hinges on cell-mediated immunity. In both infections, macrophages are the primary host cells harboring the bacteria, and T-lymphocytes orchestrate the activation of these macrophages to kill or contain the pathogens.[25]

Macrophage Interaction:

Nocardia are facultative intracellular organisms; upon inhalation or entry, they are phagocytosed by alveolar macrophages. Virulent *Nocardia* strains have evolved mechanisms to persist inside

phagocytes. One key virulence trait is the inhibition of phagosome–lysosome fusion inside macrophages, analogous to *M. tuberculosis*. Beaman et al. (1980) showed a direct correlation between a *Nocardia* strain's ability to block phagolysosomal fusion and its virulence in mice. Additionally, *Nocardia* can reduce macrophage lysosomal enzyme levels (like acid phosphatase) when surviving intracellularly, thereby subverting bactericidal mechanisms[8]. Rabbit alveolar macrophages, studied in vitro, are capable of ingesting *Nocardia* and can kill a proportion of the bacteria, especially the more fragile filamentous forms of *Nocardia*[8]. However, coccoid forms (smaller, rod-shaped cells from the same culture) tend to be hardier inside macrophages. These findings highlight that the stage of bacterial growth affects *Nocardia*'s fate in macrophages – information derived from in vitro assays with rabbit cells. In live hosts, once infection is established, activated macrophages are crucial for containment. Activation is primarily induced by T cell cytokines (e.g. interferon-gamma, TNF-alpha). In rabbit TB models, an early peak in TNF-α production by macrophages and T cells was associated with clearance of bacilli from lungs[26]. If similar dynamics hold for *Nocardia*, one would expect that a robust initial pro-inflammatory response is needed to curb the infection.

T-Lymphocytes:

Cell-mediated immunity against *Nocardia* has been demonstrated predominantly in mouse studies. Classic experiments showed that mice lacking T cells (or with T cell suppressed) cannot effectively control *Nocardia* infection, whereas B cell-deficient mice can. T cells mediate protection through two major functions: (1) releasing cytokines (like IFN-γ) to activate macrophages (the Th1 response), and (2) direct cytotoxicity against infected cells. A remarkable finding by Deem et al. (1983) was that *Nocardia*-sensitized T cells can directly bind to and kill *Nocardia* organisms in vitro, suggesting a possible lymphocyte-mediated microbicidal effect in addition to classical macrophage activation. This direct T-cell killing (sometimes called "non-traditional cytotoxicity") is less well-known but indicates how essential T cells are in nocardial defense[27], [28]. In rabbits, while direct studies are lacking, there is evidence from TB models: rabbits that achieve latent TB have an early activation of CD4 and CD8 T cells in lungs and draining lymph nodes, correlating with control of bacterial growth[29]. We can extrapolate that an effective Th1 response in rabbits would similarly be required for *Nocardia* containment. Indeed, *Nocardia* cell wall components (e.g. trehalose dimycolate analogs) are known to be strong immunostimulants that can provoke T-cell responses in other species.

Cytokine Profile:

Though detailed cytokine studies in rabbit nocardial infection are not reported in literature, insights from mice and humans suggest that a Th1-dominant cytokine milieu is key. High levels of IFN-γ, IL-12, and TNF-α promote macrophage killing of *Nocardia*. Mice experimentally infected with *N. asteroides* showed that neutrophils producing IFN-γ and IL-17 were rapidly recruited to infection sites and contributed to bacterial clearance. IL-17 (from Th17 cells and γδ T cells) aids in mobilizing neutrophils via chemokine CXCR2 signaling, an axis proven important in early anti-*Nocardia* defense. Rabbits have the homologous capacity for IL-17 production and neutrophil recruitment, so it is plausible that these mechanisms would also occur in rabbit

nocardiosis[30]. On the other hand, a skew toward Th2 or regulatory cytokines might impair clearance. In chronic mouse nocardiosis, a shift to an immunosuppressive microenvironment has been observed: increased IL-10 and TGF-β, with expansion of regulatory T cells, allowing *Nocardia* to persist longer. It is not yet studied if rabbits undergo a similar immune shift during prolonged infection, but given rabbits' tendency to clear *Nocardia* quickly, an interesting hypothesis is that rabbits might inherently mount a stronger Th1 response with less prone to regulatory dominance, contributing to their resistance.[31], [32]

Innate Immune Cells:

In addition to macrophages, neutrophils and dendritic cells are important. *Nocardia* is known to induce a robust acute neutrophilic response. Neutrophils can phagocytose *Nocardia*, but virulent strains often resist neutrophil killing (even though neutrophils generate oxidative bursts). Chronic granulomatous disease (CGD) patients, who have defective neutrophil oxidative burst, are notoriously susceptible to severe nocardiosis, underlining the role of reactive oxygen species in controlling *Nocardia*. In rabbits, neutrophils are a first line of defense as well; however, detailed studies of rabbit neutrophils vs. *Nocardia* were not found in the literature, representing another gap. Dendritic cells in humans respond to *Nocardia* by producing IL-12 and IL-23, polarizing T cells toward Th1 and Th17 pathways[33], [34]. We expect rabbit dendritic cells to function similarly, although this has not been specifically documented for *Nocardia*.

In summary, robust cell-mediated immunity – primarily Th1/Th17 responses and activated macrophages – is indispensable for fighting *Nocardia*. Rabbit models of TB indicate that these animals are quite capable of mounting such responses (leading to control or even sterilization of infection). Therefore, we infer that rabbits likely use analogous mechanisms against *Nocardia*, even if not experimentally verified. The deficit of **direct immunological studies in rabbits** (e.g. measuring cytokines, T-cell subsets during nocardial infection) is evident. Filling this gap would require controlled infection experiments in rabbits (possibly using a sufficiently virulent *Nocardia* strain or transient immunosuppression to allow establishment of infection to study the ensuing immune reaction).

B Cell and Humoral Immune Responses

While cell-mediated immunity is central to controlling *Nocardia* and *M. tuberculosis*, the role of B cells and antibodies (humoral immunity) in these infections has been controversial and understudied – especially in the case of *Nocardia*. Historically, *Nocardia* research has suggested that B lymphocytes and antibodies play little protective role. Experiments in mice by Rico et al. demonstrated that B-cell deficient mice (engineered to lack antigen-specific B cells) were not more susceptible to *N. brasiliensis*; in fact, they controlled the infection as well as normal mice. Moreover, providing exogenous anti-*Nocardia* antibodies to normal or T-cell–deficient mice did not improve outcomes – it actually worsened the disease, leading to larger lesions and bone destruction in a footpad infection model[35], [36]. The authors concluded that antibody responses

can be detrimental, possibly by opsonizing *Nocardia* in a way that enhances their uptake by phagocytes without killing (facilitating spread, or causing immune complex damage). Consistently, Beaman et al. noted that certain anti-*Nocardia* antibodies could be "detrimental to the host and contribute to disease". These findings formed a paradigm **that humoral immunity is not protective in nocardial infections,** which starkly contrasts with many other bacterial diseases where antibodies are beneficial.[10], [37]

In rabbits, there is virtually no direct data on B cell responses to *Nocardia*. No studies were found that examine, for example, antibody titers in rabbits infected with *Nocardia* or the effect of B-cell depletion on a rabbit's ability to handle the infection. Given rabbits are often used to raise antibodies (e.g. for diagnostics), one could speculate that rabbits can produce antibodies against *Nocardia* antigens if infected or immunized, but whether these antibodies aid in clearance is an open question. The research gap here is clear: *the role of B cells and antibodies in rabbit nocardiosis remains unaddressed*. This is important not only for basic understanding but also for translational aspects like vaccine design .

It's worth noting some nuance from more recent research: Not all antibody responses are equivalent. A study in 2009 by Gonzalez-Suarez et al. found that in a mouse *N. brasiliensis* footpad infection (modeling actinomycetoma), passive administration of a specific IgM monoclonal antibody led to reduced bacterial burden and disease severity, whereas an IgG antibody did not confer protection[25], [38], [39] . IgM, being pentameric, might promote agglutination of bacteria and enhance phagocytosis in a way that results in their destruction, or activate complement more effectively, whereas certain IgG might just opsonize bacteria for uptake but not killing. This indicates that some humoral responses could have a protective effect under specific circumstances, challenging the blanket notion that antibodies are always harmful in nocardiosis. In tuberculosis, similarly, the traditional view has been that antibodies are unhelpful; however, recent studies in TB have begun to explore potential roles for antibodies (e.g. opsonizing *M. tuberculosis* to modulate macrophage responses). There is emerging interest in "protective antibodies" in TB, though it remains an area of debate.

For rabbits, given their relative resistance to these infections, one might hypothesize that antibodies are not the key factor in their immunity (likely T cells are). Nonetheless, rabbits do develop lymphocyte-rich granulomas which include not only T cells but also B cells in the peripheral cuffs. Histologically, granulomas often have peripheral B-cell follicles or aggregates in both human and animal TB. The presence of B cells in the granuloma milieu raises questions about their function: Are they producing locally some immunoglobulins? Do they act as antigen-presenting cells supporting the T-cell response? Or are they largely bystanders? These questions remain unanswered in rabbit models.

From a clinical perspective, humoral immunity in nocardiosis and TB has not been shown to confer reliable protection, which is why there are no antibody-based therapies or widely used vaccines leveraging antibodies for these diseases so far. However, autoantibodies or hypergammaglobulinemia could contribute to immune complex deposition and tissue damage in chronic disease. If rabbits were studied, one might check for immune complex-related pathology in chronic nocardial lesions (as seen in immune complex glomerulonephritis in chronic infections). This too has not been reported but is another angle to consider.

In summary, B cell responses and humoral immunity represent a significant knowledge gap in the context of rabbits infected with *Nocardia*. The consensus from other models is that they are not central to protection and can even exacerbate disease, but this is based on limited data. Future rabbit studies could directly test this – for example, by experimentally infecting normal vs. B cell–depleted rabbits (if a model of infection is established) to see differences, or by characterizing the antibody isotypes generated during infection. Bridging this gap could uncover whether rabbits have any unique antibody-mediated mechanisms that contribute to their resistance, or confirm that cell-mediated mechanisms are solely responsible.

Genetic Susceptibility and Host Factors

Genetic factors can profoundly influence the outcome of infection with *Nocardia* or *M. tuberculosis*. In humans, certain inborn errors of immunity (like mutations in the IFN-γ/IL-12 axis, as well as the NADPH oxidase in CGD) dramatically increase susceptibility to mycobacterial diseases and nocardiosis, underscoring those pathways' importance. Beyond rare mutations, population studies have identified various polymorphisms (in genes such as *NRAMP1 (SLC11A1), TLR2, TNF-α, VDR* etc.) associated with differing TB susceptibility in humans.[40], [41]

In rabbits, far less is known about genetic susceptibility for these infections. Rabbits are outbred (e.g. New Zealand White) or partially inbred in research settings, but not to the same extent as mouse strains. There have not been, to our knowledge, dedicated studies selecting rabbit lines for high or low susceptibility to *Nocardia* or TB to identify responsible genes. The matrix in Figure 5 assigns a very low score for "Genetic Susceptibility" research in rabbit models (1 out of 10) – indicating virtually no coverage in the literature. By contrast, human studies in this area (e.g. looking at human genetic predispositions to TB) are somewhat more numerous (score 4/10), and even mouse models have some data (score 2/10, e.g. identification of the sst1 locus in mice that affects TB lesion necrosis).

One known aspect is that rabbits are inherently more resistant to *M. tuberculosis* than guinea pigs or certain mouse strains. This species-level trait suggests that rabbits have genetic or physiological factors that confer greater resistance. For example, rabbits mount strong early immune responses that clear bacilli or limit their growth, possibly linked to genes regulating inflammatory responses[42], [43]. It's plausible that rabbits might express higher baseline levels of certain cytokines or possess more effective macrophage antimicrobial machinery (like inducible nitric oxide synthase activity) compared to more susceptible species. These possibilities remain speculative without targeted research.

Interestingly, within rabbits, the few available inbred strains (e.g. the USDA strain, Japanese White rabbits, etc.) have not been systematically compared for infection outcomes. If such differences exist, they could be exploited to find genetic loci associated with susceptibility. Additionally, modern genomic tools like genome-wide association studies (GWAS) or CRISPR gene editing in rabbits (which is increasingly feasible) could be used to probe specific gene functions in immunity. None of this has been reported yet for *Nocardia* or TB in rabbits.

Host factors beyond genetics also play a role. These include age, sex, and immune status. For example, younger rabbits might be more susceptible to certain infections due to an immature immune system, although this hasn't been specifically shown for *Nocardia*. Nutritional status or co-infections could also affect outcome. In humans, malnutrition or HIV co-infection greatly increase TB risk; in rabbits, experimental immunosuppression (via corticosteroids) clearly converts a contained *Nocardia* infection into a fulminant one[44], [45]. This aligns with the notion that an intact immune system is critical, and that genetic or acquired immunodeficiencies tip the balance in favor of disease. Another host factor to consider is microbiome or commensals, which can modulate immune responses (though no data specific to rabbits and nocardiosis exist).

Overall, the genetic and host susceptibility factors remain an open frontier in rabbit models. Identifying such factors is important for a couple of reasons: (1) It could help in developing improved models – e.g. a genetically susceptible rabbit line that reliably develops disease might be useful for experimental studies or testing interventions. (2) It can inform human health by validating whether certain immune pathways are universally important across species. For instance, if rabbits with a hypothetical knockout of IFN-γ or TNF-α signaling were generated, they would likely become highly susceptible to *Nocardia* and TB, reinforcing the critical nature of those cytokines (mirroring human and mouse data). In conclusion, genetic susceptibility is recognized as significant in principle but is largely unexplored in rabbits for nocardial and TB infections. This is a noteworthy gap: future research that explores rabbit genomics and immunogenetics could uncover why rabbits handle these infections relatively well and whether we can leverage those insights for therapeutic benefit (for example, are there rabbit-specific antimicrobial factors that could be mimicked or enhanced in humans).

Conclusion :

Rabbit models have contributed significantly to our understanding of granulomatous infections, confirming the importance of Th1 immunity and granuloma structure in containing pathogens like *Nocardia* and *M. tuberculosis*. However, to fully leverage this model and improve translational relevance, further research must address the gaps in humoral immunity and genetic susceptibility. By answering the open questions posed, we can better interpret rabbit data in the context of human disease and perhaps improve interventions. The ultimate goal is that insights gained from rabbits will help shape vaccines or therapies that enhance host defense (for example, boosting T-cell immunity in immunocompromised patients at risk of nocardiosis, or modulating detrimental antibody responses). Additionally, understanding why rabbits rarely progress to severe disease could inspire novel approaches to prevent TB patients from developing progressive, damaging granulomas. Thus, *the humble rabbit, often overlooked in modern immunology, may yet unlock new strategies to combat old foes like tuberculosis and opportunistic infections like nocardiosis*.

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