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Cytokine Profiles and Lesion Immunopathology in Sheep with Cystic *Echinococcosis*

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Abstract

Background: Cystic echinococcosis (CE), a parasitic disease caused by *Echinococcus granulosus*, remains one of the most important neglected zoonotic diseases in sheep-producing regions, where infected animals act as major intermediate hosts and sustain transmission to dogs and humans. In sheep, the disease is not only a parasitic cystic condition but also a complex immunopathological process shaped by parasite viability, cyst fertility, organ tropism, cytokine polarization, and chronic tissue remodeling.

Aims: This narrative review discusses the assessment of cytokine-related gene expression together with histopathological changes in sheep infected with CE. Attention has been paid to the local balance between T helper (Th) cells such as Th1, Th2, Th17, and regulatory immune pathways including interferons (IFN), tumor necrosis (TNF), interleukins (IL), and transforming growth factor (TGF) (e.g., IFN-γ, TNF-α, IL-1β, IL-4, IL-6, IL-10, IL-17A, TGF-β), and related innate signaling mediators.

R**esults**: Furthermore, the review has connected molecular expression patterns with classical liver and lung lesions (e.g., granulomatous inflammation, fibrosis, adventitial layer formation, necrosis, vascular congestion, eosinophilic infiltration, macrophage activation, and cyst wall remodeling).

Conclusions: The current review discussed the recent studies on hydatid fluid, extracellular vesicles, parasite microRNAs, protoscolex transcriptomes, and genotype-associated pathology which were integrated to propose a modern tissue-based model of ovine disease. Overall, this narrative review indicated that combined cytokine gene expression and histopathology can

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improve disease staging, cyst viability interpretation, vaccine evaluation, and biomarker discovery in sheep.

Keywords: Cystic echinococcosis, Cytokines, Gene expression, Histopathology, Sheep

Introduction

Cystic echinococcosis (CE) is a parasitic disease caused by the larval metacestode stage of *Echinococcus granulosus*. In endemic transmission cycles of this parasite, sheep are the most prevalent intermediate hosts. The classical dog–sheep cycle increases environmental contamination by preserving parasite eggs and increases the economic burden through inappropriate use of livestock due to the condemnation of organs, decreased productivity, and persistent zoonotic hazards. Recently, it has been proposed that the disease is still greatly underestimated due to the lack of evident clinical signs in the majority of infected livestock before slaughtering. The silent signs of the disease enable cysts to remain in the environment for a prolonged period (Yasen *et al*.,2021). Additionally, the sheep and buffalo strains(G1 and G3) genotypes are correlated to sheep and cattle, and important issues of regional transmission, vaccination, and public health are involved (Yang *et al*.,2021). Therefore, in sheep, CE should be seen as a veterinary production issue and as an important example of a chronic host–parasite coexistence and adaptation problem (Pertone *et al*., 2024).

The immune response toward hydatid cysts is complex. It is dependent on cyst ealge, cyst fertility, cyst localization, the leakage of parasite antigens, and the immune reaction of host tissues. In the early host immunity, there can be the presence of some Th1 immunity signals (e.g. IFN-γ, TNF-α, and IL-12), and in the later phases, there can be the presence of IL-4, IL-10, and TGF-β (Jesudoss Chelladurai *et al*., 2024). In recent studies concerning hepatic CE, active and inactive cysts are also associated with various Th1, Th2, and Th17 immune responses in the various stages of the cysts. This resulted in the hypothesis that Th1, Th2, and Th17 immune responses can be used to assess cyst activity and provide a clearer understanding of the evolution of cysts and the reasons behind the viability/dormancy of the cysts (Kheninef *et al.*,2024) In studies that were performed on sheep using hydatid fluid extracellular vesicles, it was found that parasite-derived vesicles can infiltrate sheep peripheral blood mononuclear cells and can alter the expression of immune-related genes such as IL-10, TNF-α, IRF-5, IL-1β, IL (Yang *et al*., 2024).

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The immune response is documented by tissue histopathology. Sheep infected by *Echinococcus granulosus* develop hydatid cysts which are encapsulated by fibrous material and infiltrated by macrophages, lymphocytes, eosinophils, and inflammatory cells in addition to degenerative and necrotic lesions in the liver and lung. Recent histopathological findings on livestock have reported pulmonary and hepatic lesions due to cysts characterized by tissue compression, inflammatory infiltrates, hemorrhage, edema, and fibrosis (Yang *et al*., 2023). These findings highlight the importance of linking microscopic lesions with cytokine expression, instead of treating pathology as a descriptive endpoint. When histopathology and gene expression are analyzed, tissue lesions gain meaning beyond structural abnormality, for example immune tolerance, immune avoidance in parasites, and tissue repair (Pereira *et al*.,2022). The necessity of developing a thorough approach to diagnosis, treatment, and research on ovine CE is clear, as it holds promise for more definitive options. The review also connects molecular expression patterns with classical liver and lung lesions, including granulomatous inflammation, fibrosis, adventitial layer formation, necrosis, vascular congestion, eosinophilic infiltration, macrophage activation, and cyst wall remodeling. Recent studies on hydatid fluid, extracellular vesicles, parasite microRNAs, protoscolex transcriptomes, and genotype-associated pathology are integrated to propose a modern tissue-based model of ovine disease.

The purpose of this review describes the association between the expression of cytokine-related genes and lesion immunopathology in *Echinococcus granulosus* infected sheep. It attempts to elucidate the roles of Th1, Th2, and Th17, as well as the regulatory and innate immune systems, on cyst viability, fertility, organ tropism, and the predominant histopathological alterations in the hepatic and pulmonary lesions. It also attempts to correlate the molecular patterns of the immune response with the tissue patterns of granulomatous inflammation, fibrosis, necrosis with eosinophilic infiltration, macrophage activation, vascular congestion, and cyst wall remodeling.

Immune landscape of ovine CE

The immune landscape of ovine CE forms from the dynamic tension of host-parasite interactions. When the parasite oncosphere completes its migration through the intestinal barrier and establishes itself in the target organs (e.g., the liver or lung), various host immune responses are initiated. These include the innate recognition response coupled with the complement system, recruitment of macrophages, and localized inflammatory response. While the formation of hydatid cysts occurs on the backdrop of acute bacterial infections, these cysts resist destruction while generating a form of immune protection within the host. The parasite reshapes the cytokine environment which may also explain the persistence of the parasite in the cyst. The early stages

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of inflammation may be characterized by TNF-α, IL-1β, IL-6, and IFN-γ; however, in chronic inflammatory conditions, IL-10 and TGF-β predominate. In chronic inflammation, these cytokines will reduce the injurious effects of inflammation on host tissues, but they will also promote the persistence of the parasite (Jesudoss Chelladurai *et al*.,2024; Kheninf *et al*.,2024). In sheep, it has been established that the hydatid cyst fluid contains extracellular vesicles that affect cytokine-associated gene expression in peripheral blood mononuclear cells (PBMCs), demonstrating that products of the parasite can modulate the immune response systemically, even outside the lesion (Yang *et al*.,2024). As such, the strongest model of the immune response to CE should encompass the entirety of the 'shifting immune spectrum' of the disease rather than the pervasive manifestation of a single Th1 or Th2 polar response. This is especially true given the degree of cyst fertility, cyst degeneration and the location of the cysts within the host may dictate the character and degree of inflammatory infiltrate (Pereira *et al*., 2022; Hidalgo *et al*., 2021) (Figure 1).

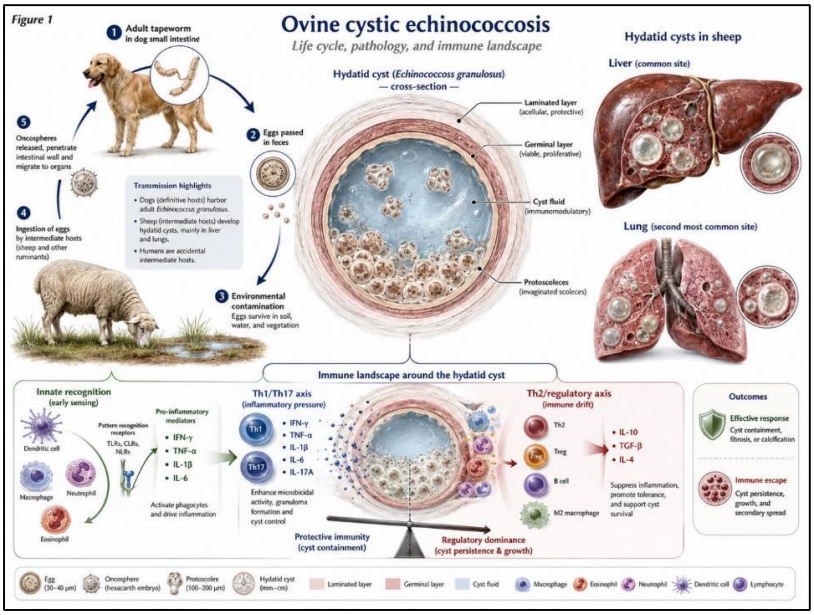

Figure 1: Ovine Cystic Echinococcosis Life Cycle and Immune Response. This figurewere generated with the assistance of ChatGPT artificial intelligence tools to illustratethe life cycle of *Echinococcus granulosus* and its preferred organs in infected sheep. Echinococcosis-infected dogs spread out the parasite eggs on the grass. Then, sheep graze on parasite-infested pasture. After ingestion, oncospheres migrate through the intestines to the liver, where they form hydatid cysts. Cysts may also appear in the lungs.. The figure also shows the immune response in infected sheep. This response begins with the innate immune system and macrophages and dendritic cells. This is followed by an organized inflammatory response dominated by Th1 and Th17 cytokines, and finally by Th2 cytokines. The Th2 cytokines induce and sustain fibrosis. Other effects of Th2 response are immune modulation and chronicity, which facilitate lesion development and the persistence of hydatid cysts.

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Given that every microscopic pattern likely corresponds to a distinct type of immune pressure, cytokine-related gene expression can be used as a molecular reflection of lesion activity in infected sheep. For instance, a cyst that is surrounded by dense mononuclear inflammation can express higher amounts of IFN-γ and TNF-α, IL-1β, and IL-6. In contrast, a cyst that has a well-organized fibrotic capsule, indicating prolonged viability, can express IL-10 and TGF-β more strongly. While the inactive cysts in human hepatic CE are associated with the Th1 and Th17 responses, it is the active cysts that are more associated with the Th2-type cytokines. Therefore, the same principle can be applied in the interpretation of ovine lesions (Kheninef *et al*., 2024). The hydatid fluid vesicles have been shown to alter the IL-10 and TNF-α levels, and also alter the TLR4-related mediators in sheep PBMCs. This indicates that secretions of the parasite can induce an inflammatory response that is not only at the protein level, but also at the level of gene expression (Yang *et al*., 2024). Therefore, quantitative polymerase chain reaction (qPCR) based cytokine profiling should not be performed in isolation and should be integrated with histological scoring that assesses the cyst wall and evaluates the inflammatory response, the degree of fibrosis and necrosis, ecto- and endo-cytosis, and vascular changes (Yang *et al*.,2023; Pereira *et al*.,2022; Pereira *et al*.,2024 ; Hidalgo *et al*., 2021). This would enable the classification of lesions as inflammatory-active, regulatory-tolerant, fibrotic-contained, or degenerative-calcifying (Baquedano *et al*.,2025) (Figure 2).

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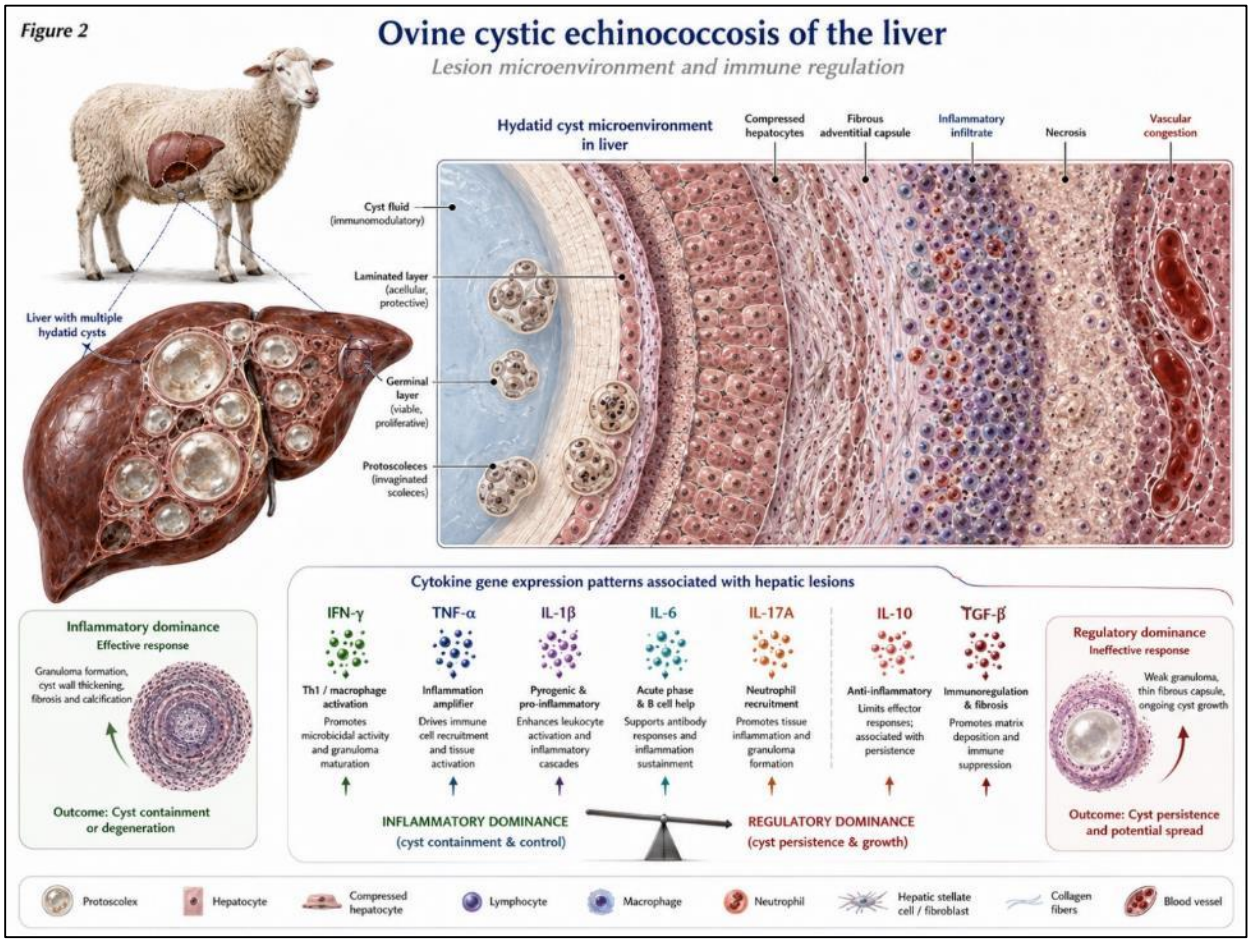

Figure 2. Microenvironment of Hepatic Hydatid Cysts and Lesions of *E. granulosus*. This figure were generated with the assistance of ChatGPT artificial intelligence tools to depicts the cysts formed in the liver and the lesions they cause. The first step is the formation of cysts and the subsequent compression of hepatic tissue. The inflammatory response to these cysts also leads to necrosis of the hepatic tissue and an increase in vascular congestion. Cysts formed during ovine echinococcosis may also trap oncospheres in the liver. This figure correlates the lesions in the liver caused by *E. granulosus* with the immune response of the host sheep and the inflammatory and regulatory cytokines in the liver of sheep infected by *E.granulosus*. The inflammatory and regulatory cytokines cause fibrosis in the liver and facilitate the formation of hepatic cysts in sheep.

Liver lesions and cytokine polarization

When it comes to the development of a cyst and the formation of an immune response to it, the liver is one of the first organs that will begin to filter the migrating oncospheres. In ovine hepatic CE, lesions can include (but are not limited to) pressure atrophy of hepatocytes, formation of a fibrous capsule, necrotic foci, a reaction of the bile ducts, congestion in blood vessels, and

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eosinophilic infiltration of diverse intensity. These alterations are not caused solely by the mechanical expansion of the cyst. Changes in cytokine patterns influence the activity of macrophages, fibroblasts, and the deposition of collagen and the organization of granulomas. The previously performed gene-expression studies of the ovine liver have shown that certain infections are capable of changing the transcriptional programs of the hosts and modifying the immune response to the infection and the remodeling of the tissue (Khorsavi *et al*., 2023). This supports the theory that hepatic CE is an active disease process at the molecular level, as opposed to a disease process that is cystic in form and created in a passive way. IL-10 and TGF-β may avoid excessive damage to the liver, along with the expression of these cytokines for a prolonged period, may create a state of tolerogenic response and may lead to the persistence of the cyst in the liver. IFN-γ, TNF-α, and IL-17A are the opposite, and may amplify the inflammatory process to the destruction of the cysts, that are no longer viable, and are degenerating. This is likely the reason that some of the lesions in the liver have a strong granulomatous and necrotic reaction (Kheninef *et al*., 2024) (Figure 3).

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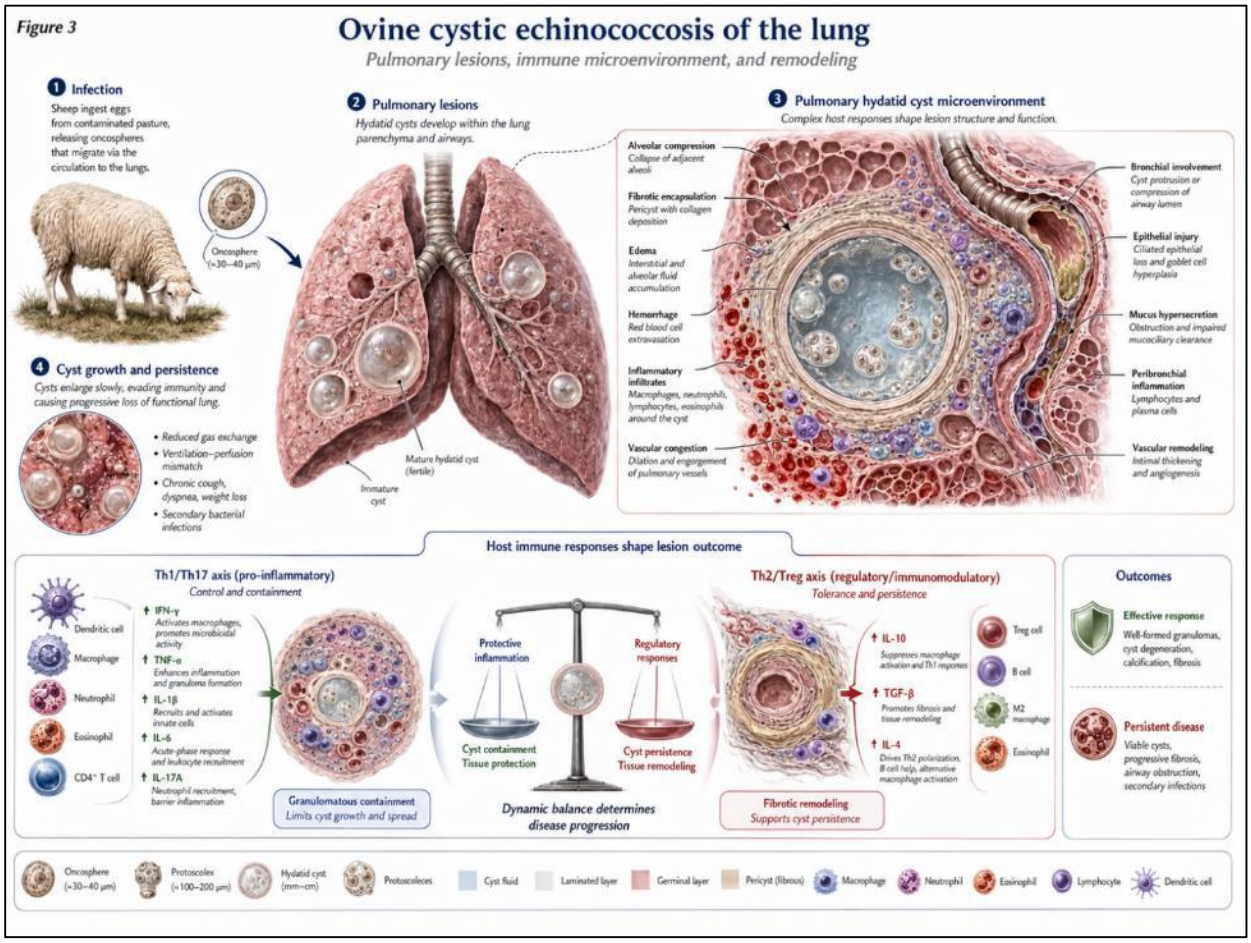

Figure 3. Pulmonary Hydatid Cysts, Immune Remodeling, and Disease Outcomes. This figure were generated with the assistance of ChatGPT artificial intelligence tools to captures the progression of pulmonary hydatid cysts following the translocation of parasites into the lungs. It covers the range of pulmonary pathologies, including compression of alveoli and interstices, congestion, edema, atelectasis, and bronchial inflammation brought on by cyst expansion. It also shows the structural type of ovine cystic echinococcosis and highlights lung tissue, which differs from liver tissue, having a gross and immune structural milieu that is still special. The immune landscape demonstrates the ongoing interplay between the various types of inflammatory responses and Th2 responses that may favor tissue remodeling and ultimately contribute to the development and persistence of chronic pulmonary lesions.

Lung lesions and respiratory immune remodeling

One more important site of ovine cystic echinococcosis (CE) is the lungs. Here, pulmonary cysts can evoke a different tissue response compared to hepatic cysts. This response depends on the organ's structure, composition of blood, and gaseous exchange. Different types of lesions in the

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lungs can be the result of histological compression of the alveoli, interstitial tissue thickening, congestion, and bleeding. Furthermore, edema, atelectasis, bronchial inflammation, and the fibrous encapsulation of cysts can be present. Recent studies have suggested that the remodeling of tissues and structures of the lungs caused by cysts is strong evidence that CE in the lungs is a chronic pulmonary disease (Yang *et al*.,2023). There can be a difference in the expression of cytokines in the lesions of the lungs and livers. This depends on the population of macrophages, the activation of the dendritic cells, and the epithelial repair pathways that differ in the respective organs. It has been shown that hydatid antigens can lead to the type of immune responses observed in the airways of IL-4, IL-5, IL-10, IL-17, and IFN-γ, thus demonstrating that parasite products are agents of inflammation in the lungs (Yang *et al*.,2023). It is urged that IL-1β, TNF-α, IL-6, IL-10, TGF-β, and IL-17A should be studied comparatively in the lungs and livers of sheep in order to identify the cytokine profiles in pulmonary and hepatic cysts (Zhou *et al*., 2019) (Figure 4).

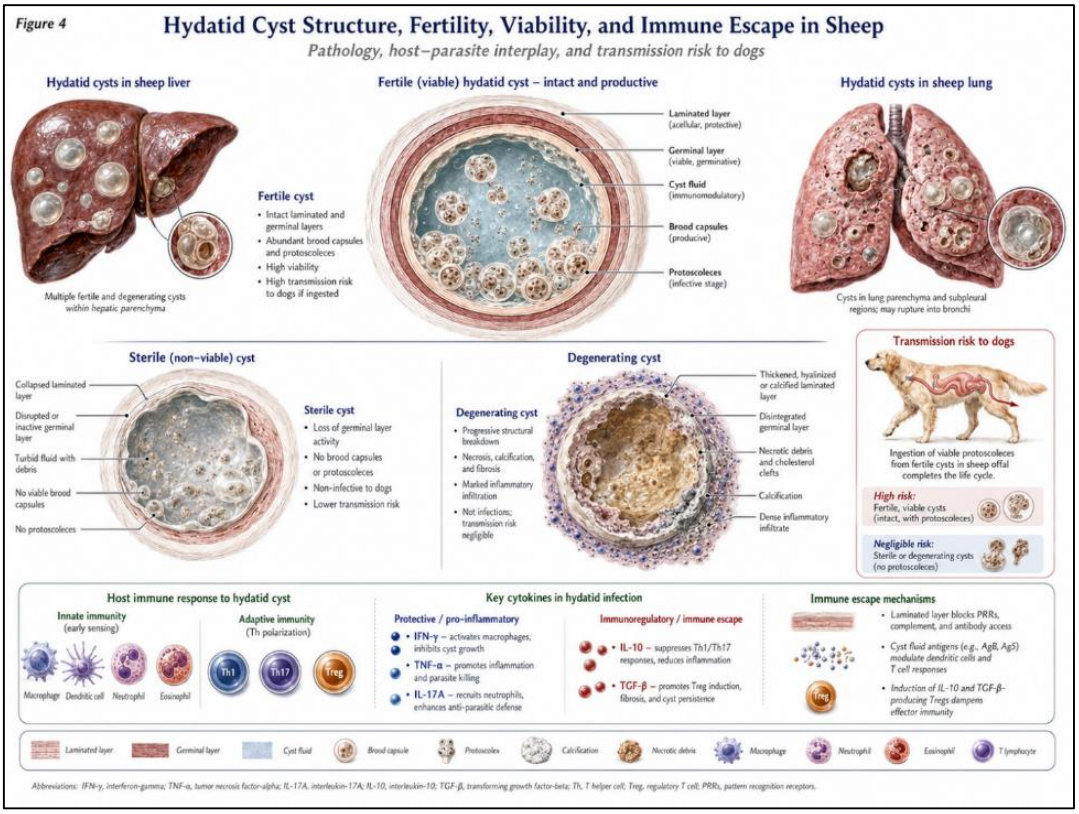

Figure 4. Structure of Hydatid Cysts and Sheep, Fertility, Viability, and Immune Evasion. This figure were generated with the assistance of ChatGPT artificial intelligence tools to captures the major structural components of the hydatid cyst including the laminated and germinal layers, cyst fluid, brood capsules, and protoscoleces. It further

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provides a summary of the major biological processes determining cyst fertility, participation in the immune response, cyst viability, and degeneration. Organ tropism is linked to the viability of fertile cysts in sheep; if the infected organ is consumed by a dog, the life cycle of the parasite is maintained. The immune landscape highlights the varying degrees of immune response from regulatory cytokines associated with viable cysts to inflammatory responses including Th1 and Th17 associated with tissue damage and necrosis.

Th1 signaling and cyst containment

Th1 signaling typically describes mechanisms involving parasite containment, macrophage activation, production of nitric oxide, and inflammatory pressure directed at the viable metacestodes. In this context, IFN-γ and TNF-α are key players, and their presence can suggest that the host is trying to limit the growth of the cysts, and to boost their degeneration. In patients with hepatic CE, it was noted that Th1-type cytokines were present around the inactive cysts, and this finding suggests that the cell-mediated immune response is likely to be the reason for the cysts being damaged or losing their viability (Kheninef *et al*.,2024). In sheep, the use of the recombinant P29 sheep vaccine studies resulted in the induction of IFN-γ. This finding provided further evidence for the protective role of Th1-related immunity within ovine echinococcosis (Nicolao *et al*.,2014). However, the strong activity of Th1 may result in tissue damage, necrosis, as well as the formation of granulomas in the cysts that are leaking and degenerating and in surrounding tissues. It is for these reasons that the presence of IFN-γ and TNF-α should be interpreted in conjunction with the histological context of cyst tissue viability and the associated inflammatory response and destruction of the tissue. A useful model for the review would be to consider that Th1 signaling presents a two-sided response: control of the parasite is positively beneficial, and so too can the inflammation be, provided it is of a poor regulation and control (Lin *et al*.,2021) (Figure 5).

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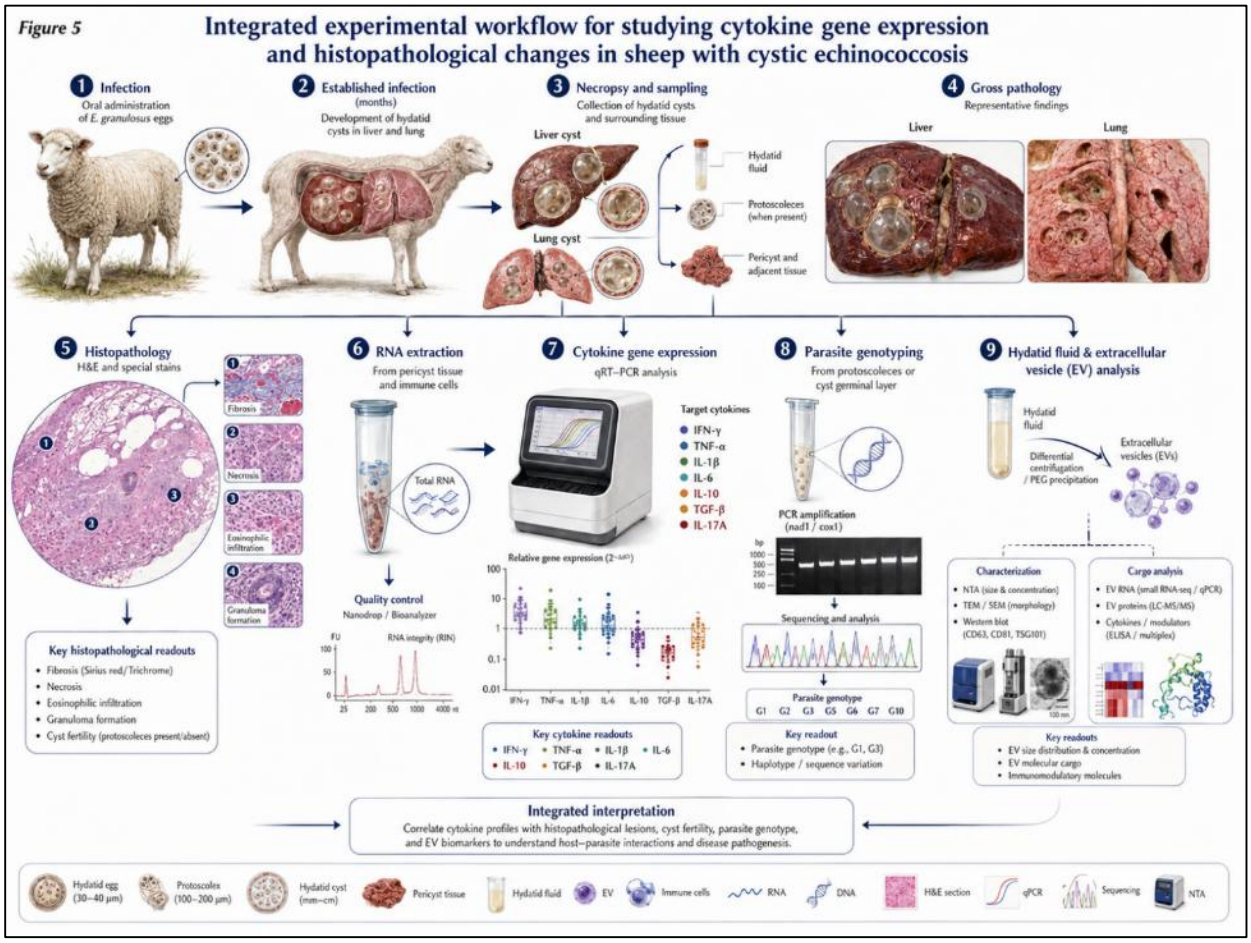

Figure 5. Proposed experimental protocols on cytokine gene expression and histopathological changes in Cystic Echinococcosus-infected sheep. This figure were generated with the assistance of ChatGPT artificial intelligence tools to demonstrates workflows for the collection or identification of infected sheep and the collection of liver and lung cysts. This includes a preliminary assessment of the fertility and viability of the cysts, which will also be sampled. The cyst sample includes the cyst wall, and the adjacent and normal, non-infected tissue of the host, as well as, the hydatid fluid and blood, if available. The figure outlines the laboratory procedures that correlate organ tropism and immune pathology. The procedures include histopathological examinations, RNA extractions, and the cytokine profiling via qPCR, as well as parasite genotype determination and the analysis of hydatid fluid or extracellular vesicles. The integration of all findings will be statistical in nature. This framework cytokine expression with histological lesion scores, which will include assessment of tissue fibrosis and necrosis, and the assessment of cellular inflammatory infiltrates, as well as the possible vascular changes, cyst viability, and the assessment of disease outcome.

Phenomenological studies of hydatid disease indicate that Th2 and regulatory cytokines remain vital for sustained cyst derangement. This largely relates to the ability of these cytokines to

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prevent the destructive inflammatory response and facilitate the establishment of inflammatory permissive microenvironments. For instance, IL-4 is believed to enhance eosinophil and humoral responses, whereas IL-10 and TGF-β are known to inhibit macrophage and Th1 response hyperactivity. Research on the local immune responses surrounding hydatid cysts has reported the up-regulation of Th2 and regulatory cytokines, particularly IL-10 and TGF-β, in the tissues adjacent to the cysts, suggesting that these viable cysts are encased in a tissue niche that offers immune protection (Baquedano *et al*.,2025).

In simple terms, hydatid lymph and some molecules derived from the cyst are able to diminish the inflammatory responses of macrophages and also disrupt NF-κB and MAPK pathways, which may help to explain why parasites are not completely eluded by the immune system (Wang *et al*., 2024). It is likely that in sheep the regulatory pattern is of a greater concern, as in order for the cysts to be shed to the dogs, they must remain viable. The balance of this immune response is associated with the presence of a mature fibrous capsule, minimal inflammation, necrosis, and considerable immunity to the damaged tissue. Thus, in this regard, IL-10 and TGF-β are among the primary indicators of the accommodation of cysts and chronicity of the response (Hamad *et al*., 2024).

Th17 axis, neutrophilic pressure, and cyst decomposition

The Th17 axis focuses on CE due to neutrophil recruitment, inflammatory amplification, and tissue remodeling, with IL-17A hypothesized to link these phenomena in chronic parasitic infections. Enhanced IL-17A and IL-17B in hydatid disease show Th17 pathway activity in cyst-associated inflammation (Baghezza *et al* ., 2025). In cases of hepatic CE, active Th17-type cytokine expression correlated with non-active cysts, suggesting that IL-17 may bring about cyst decomposition, or inflammatory control (Kheninef *et al*.,2024). Sheep vaccination studies also reported that recombinant P29 brought about the release of IL-17A and IFN-γ, thus supporting the protective immunity hypothesis of a combined Th1/Th17 response (Nicolao *et al*., 2019). Th17 response, histopathologically, is evident with dense inflammatory bands, non-specific inflammation, tissue irritation, and early chronic degenerative changes in the cyst wall. In the case of IL-17, there is a protective paradox, as chronic IL-17 is detrimental and causes tissue injury, and edema. In ovine studies, IL-17A, along with IL-6, IL-23, and TNF-α, and neutrophil scoring should be evaluated, to clarify if there is a protective pathway and damage (Usman *et al*.,2024).

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Macrophages, dendritic cells, and innate immune checkpoints

Macrophages and dendritic cells serve as connecting cells between cyst recognition and cytokine programming. In the case of hydatid cysts, macrophages may become activated inflammatory cells, epithelioid cells, foreign-body giant cells, or regulatory macrophages, depending on what antigens they are exposed to and what cytokine signals they receive. Localized immune investigations showed that macrophages are central to the tissue response to hydatid cysts, especially in the adventitial layer surrounding the parasite (Baquedano *et al*.,2025). Dendritic cells are also crucial because hydrated cyst fluid influences dendritic cells' function and autophagy, as well as T-cell trafficking and polarization, thereby determining if the response is primarily inflammatory, regulatory, or a combination of the two (Al-Mmasoudi *et al*., 2021). In sheep, parasite-derived vesicles modulated the expression of cluster of differentiation 14 (CD14) and IRF5 in PBMCs, indicating that they may directly influence innate immune signaling and macrophage-related pathways (Yang *et al*., 2024). Strong macrophage activity, on the other hand, is observed in the presence of granulomatous inflammation, thickening of the cyst wall, cellular cuffs, and zone of phagocytosis near necrotic membranes. Therefore, future research on ovine CE should integrate macrophage immunohistochemistry with qPCR for CD14, TLR4, IRF5, pro-IL-1β, TNF-α, IL-10, and TGF-β, in order to ascertain if macrophages are engaged in killing the parasites or if they are adopting a regulatory and tolerant stance toward the parasites (Li *et al*.,2020).

Hydatid fluid and extracellular vesicles as immunological mediators

Hydatid fluid is an immunological medium and is not merely an inert substance in the cyst. The innate immunity includes parasite proteins, metabolites, extracellular vesicles, and small regulatory RNAs. Recent studies identified several populations of extracellular vesicles in hydatid fluid and demonstrated that 110 k vesicles were taken up by sheep PBMCs and induced the expression of IL-10, TNF-α, IL-1β, IL-17, IRF5, and CD14 (Yang *et al*.,2024). Another study demonstrated that exosomal egr-miR-71 from *E. granulosus* could create immune functions with respect to PBMCs of sheep, including the regulation of cytokines and the nitrogen oxide metabolism, suggesting that the parasite microRNAs may cause remodeling of the immune system of the host (Beyhan *et al*.,2022). These findings indicate that escape from the cyst may control immune function beyond its immediate wall, and enable the formation of a chronic, low-grade local tissue response. Lesions with intact cysts and minimally encroaching aggressive inflammation may still reflect vesicle-mediated immune regulation. However, ruptured or degenerating cysts provoke a potent inflammatory response and injuries. This field holds special

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promise, as the vesicle cargo could be a resource for cyst viability, immune evasion, and vaccine target biomarker discovery (Alizadeh *et al*., 2020).

Fibrosis and adventitial layer formation

Fibrosis is a histopathological characteristic of ovine CE that conveys chronic immune regulation and tissue repair. The adventitial layer is the cyst wall and is a container of the host immune response that may consist of collagen, fibroblasts, macrophages, lymphocytes, eosinophils, and vasculature. In cattle and sheep, the adventitial layer of *E granulosus* cysts reveals characteristics of cellular distribution that are influenced by cyst fertility, cyst location in the organ, and the species of the host, which underscores the importance of the cyst wall as a meaningful immunological compartment (Hajjafari *et al*., 2024). TGF-β is a fibrogenic cytokine that is responsible for fibroblast activation and collagen deposition but also has the ability to suppress some of the more vigorous phases of the inflammatory response (Baquedano *et al*., 2025). TNF-α, IL-1β, and IL-17A are cytokines that may remain and cause fibrotic changes as a result of chronic inflammation. Consequently, fibrosis must be placed within the context of cyst status and cytokine expression and should not be documented as only "mild," "moderate," or "severe." Strong ovine studies could promote a scoring system to document cyst fertility, inflammatory cell type, capsule thickness, and collagen density in conjunction with their expressions of TGF-β, IL-6, IL-10, and IL-17A (Wu *et al*., 2024).

Cyst fertility, viability, and immune escape

Cyst fertility is of particular interest in sheep epidemiology, given that protoscoleces of fertile cysts preserve the organism life cycle after absorption of infected visceral organs by dogs. Fertile cysts may maintain different immune relationships than sterile and degenerated cysts. Transcriptomic studies on *E.granulosus* sensu stricto protoscoleces revealed that immune modulation genes in protoscoleces expressed in cysts of cattle and sheep are expressed differently, supporting that the parasite may be adjusting its mRNA repertoire to the host species and organ environment (Celik *et al*.,2024). Weighted gene co-expression analysis emphasizes the notion of viability being an active state of the cysts, with protoscoleces prioritizing the immune evasion gene clusters and parasite life cycle (Alkhaldi,2024). From the host side, fertile cysts are associated with greater production of IL-10 and TGF-β, which are described as regulatory cytokines, whereas Th1 and Th17 inflammation is described in cysts that are non-fertile and degenerated (Kheninef *et al*.,2024). From a histological perspective, viable fertile cysts tend to maintain laminated and germinal layers, while degenerated cysts may show necrosis and severe inflammation. The correlation of cyst fertility and cytokines may assist in determining the transmission risk (Jonny *et al*., 2021).

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Genotype-related variation in pathology and immune response

E.granulosus includes G1 and G3 lineages; variation within a lineage can reflect differences in geographic distribution, fertility, host preference, and G1 and G3 pathogenic behavior, and variation within a lineage can influence the biology of CE. Empirical research includes molecular studies that proved occurrence of G1 and G3 in sheep and cattle of various regions of the world and claimed the sheep–dog cycle is still the main route of its population zoonotic infections (Yang *et al*., 2021). Mitochondrial markers (nad5 and cox1) used in other studies were helpful in differentiating G1 and G3 isolates from humans, cattle, and sheep, and were relevant due to the fact that differences in lesion severity or cyst distribution are often associated with genotypes (Lan *et al*., 2025). In sheep, variation among genotypes can affect fluid composition, viability of protoscoleces, antigent release, and cytokine response. In a G1-dominant cycle, sheep can be very fertile, while in a mixed cycle, histopathological changes can be very hard to interpret. Thus, in the future, design of review and supplements studies should not consider all hydatid cysts as similar in nature. Based on molecular genotyping, histological lesion scoring, and lymph cytokine expression, it can be studied whether G1 and G3 variation influences intensity of inflammation, cyst fertility, organ tropism, and fibrosis (Al Malki and Ahmed ,2022).

Biomarker panels for diagnosing and staging ovine disease

A modern approach to diagnosing ovine CE should focus on the development of biomarkers for staged evaluation of the state of cyst activity, the state of the immune system, and the state of transmission. Traditional slaughterhouse CE diagnosis relies exclusively on detection of cysts during necropsy, while serological analysis has low to moderate sensitivity and may fail to distinguish between the presence of active versus inactive infection. Xu *et al*.(2024) describe the passive/active infection classification system based on serum fluorescence spectroscopy and machine learning (ML) and note the increased interest of researchers in non-invasive CE detection systems for sheep. However, cytokine biomarker patterns associated with different types of lesions can provide more insight. A useful ovine tissue qPCR biomarker panel may include IFN-γ, TNF-α, IL-1β, IL-6, IL-10, TGF-β, IL-17A, CD14, TLR4, and IRF5, along with a reference gene. This biomarker panel may be interpreted along with histopathological scores and cyst fertility assessments. Follow-up studies on humans have shown that activity monitoring and disease staging can be achieved using specific immune system and cytokine biomarkers, which can be used in sheep to assess the viability of cysts, identify infection of elevated risk and fertility, and determine the efficacy of vaccination and control programs. Such biomarkers would

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be especially useful in CE endemic regions where conducting routine molecular surveillance lacks feasibility (Petrone et al., 2015; De Biase *et al*., 2023).

Cytokine and histology data for vaccination studies

To develop an *Echinococcus granulosus* vaccine, researchers need to assess the protective potential of the vaccine by looking at immune protection in the target tissues. In sheep, the use of recombinant P29 to assess protection leads to the production of IFN-γ and IL-17A. Thus, the development of Th1 and Th17 is shown to aid protection against echinococcosis (Nicolao *et al*., 2019). Previous studies on the immunoprotection of P29 in sheep have also shown the importance of a combination of both cell-mediated and humoral immunoprotection, although the best immune correlates of protection are still unresolved (Wang *et al*., 2016). The help of histopathology can aid in giving answers, because a protective vaccine would be expected to reduce both the number and size of cysts and their tissue-destructive fertility and would provide inflammatory organization and clearance of necrosis and tissue destruction. The expression of cytokine genes may help to distinguish protective immunity and tissue-destructive inflammatory response. For example, a protective response may be indicated by the presence of IFN-γ and IL-17A with a reduction in cyst fertility and the presence of a severe inflammatory response with necrosis and tissue-destructive inflammation with high levels of TNF-α and IL-1β. Thus, the next trial of vaccination in sheep should be designed to assess cytokine expression at the tissue level by the use of qPCR, ELISA, and flow cytometry as well as cyst fertility assessment and histopathology scoring to determine protection at the tissue level. (Yang *et al*., 2023).

One of the more promising future studies on the relation of cytokines and gene expression to histology in sheep CE focuses on a combined molecular approach with pathology. Naturally infected sheep from abattoirs can be subdivided according to the organs infected, infertility of cysts, size of cysts, and distress of cysts. Samples should be collected from the cyst wall, nearby tissues, associated normal tissues, and blood if feasible. Cytokines and innate response markers should be assessed by qPCR, and histology should be used to assess fibrosis, necrosis, the density and type of inflammation, congestion of vessels, and the vascular response and the thickness of the capsule. Cysts should be genotyped using mitochondrial markers cox1, nad1 and nad5, as they should help explain the G1/G3 variation in relation to the observed pathology. Hydatid fluid could be examined to evaluate vesicular markers, microRNAs, and immunomodulatory proteins, especially given the evidence that vesicles and egr-miR-71 alter the immune cell responses of sheep. Statistical models should be used to relate gene expression to histology, cyst fertility, location, and organ involvement, and to genotype the data. This type of combined approach would likely be publishable in leading journals. It is likely to appeal to those

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studying field pathology, molecular immunology, the biology of parasites, and the pathology of zoonoses.

Conclusion

CE in sheep can be more accurately characterized as a dynamic immunopathological disease rather than just a simple cystic infection. The best insights are derived from the analysis of cytokine-related gene expression in conjunction with histopathological assessment, as cytokines provide an avenue to interpret the biological significance of the fibrosis, granulomatous inflammation, necrosis, eosinophilic infiltration, macrophage activity, and remodeling of cyst wall. Containment and degeneration of the cysts are possibly mediated by the Th1 and Th17 responses, while the Th2 and some regulatory cytokines may be involved in the chronic maintenance and persistence of the cysts as well as in the immune-tissue homeostasis. The presence of protoscolex immune evasion genes as well as parasite microRNAs, hydatid fluid, and extracellular vesicles can explain how the cysts remain viable and persistent in the tissues of the host sheep. The studies of the future should focus on developing an integrated approach to improve disease staging, vaccine assessment, disease biomarkers, and better understanding the sheep-dog transmission cycle as well as to clarify the organ tropism, stratify the cysts based on fertility, and carry out an analysis of the hydatid fluid and genotype the parasite.

Recommendations:

Future studies should integrate cytokine gene expression profiling with histopathological and molecular analyses to improve the understanding of cyst viability and host immune responses in ovine cystic echinococcosis. Furthermore, incorporating parasite genotyping and hydatid fluid biomarkers may facilitate the identification of reliable diagnostic and prognostic indicators. Such multidisciplinary approaches could also support the development of effective vaccines and sustainable disease control strategies.

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Conflict of interest

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