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Exploring the Mechanistic Foundations of the Long-Term Safety of IL-1β Targeted Anti-Inflammatory Therapy

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Abstract: The expanding clinical use of interleukin-1β (IL-1β) monoclonal antibodies (mAbs) for chronic diseases raises important questions about their long-term safety, particularly infection risk. Despite IL-1β serves as a central driver of inflammatory responses, multiple large-scale clinical trials have demonstrated that specific blockade of IL-1β does not substantially increase overall infection risk in patients. This review explores the mechanistic basis for this favorable benefit-risk profile. It highlights the constitutive immune mechanisms that provide a stable first line of defense independent of IL-1β induction, the high complementarity within the IL-1 family enabling selective blockade benefits, and the pharmacokinetic profiles of biologics ensuring selective lesion distribution. Furthermore, it discusses the precise neutralization of systemic spillover inflammation while preserving local autocrine/paracrine homeostasis, the evolving disease spectrum in which sterile inflammation has surpassed infection as a primary health challenge, and the need for clinical vigilance against specific pathogen infections. Overall, specific blockade of IL-1β achieves effective anti-inflammatory therapy without compromising fundamental host defense.

Keywords: IL-1β monoclonal antibodies; Long-term safety; Constitutive immunity; Sterile inflammation; Infection risk

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1. Introduction

As the clinical application of interleukin-1β (IL-1β) monoclonal antibodies (mAbs) expands from rare diseases to broader indications, such as gout and the prevention of cardiovascular events, their remarkable clinical efficacy has been robustly validated. However, the safety profile associated with long-term use, particularly the risk of infection, remains a core clinical concern. Encouragingly, multiple large-scale clinical trials have shown that specific blockade of IL-1β is associated with a generally favorable safety profile,

with only a modest increase in selected infections and no substantial increase in opportunistic infections. Elucidating the molecular mechanisms by which IL-1β mAbs achieve an optimal balance between benefit and risk is crucial for accurately identifying target populations and formulating scientifically sound treatment strategies. Here, from an immunological perspective, we systematically review why IL-1β mAbs can exert potent anti-inflammatory effects without disrupting the host's fundamental defence homeostasis, and we discuss clinical considerations essential for modern chronic disease management.

2. Constitutive immune mechanisms: The fundamental cornerstone of host defence and cytokine signaling redundancy

Clinical evidence indicates that the specific blockade of IL-1β does not significantly elevate the overall incidence of severe infections. The core mechanism underlying this safety profile lies in the existence of a constitutively active immune defence system that operates independently of pro-inflammatory cytokine induction. As reviewed by Paludan et al., the host maintains a repertoire of "always-on" basal defence mechanisms, encompassing physical barriers (skin and mucosa), the complement system, antimicrobial peptides, and constitutively expressed restriction factors. These mechanisms form the "chassis" of the immune response, functioning without the requirement for induction by IL-1β or other cytokines, thereby providing the host with its first and most stable line of defence (Constitutive immune mechanisms: mediators of host defence and immune regulation) [1].

When pathogens breach these constitutive barriers, the host initiates an inducible response characterized by cytokines such as IL-1β, TNF-α, and type I interferons (IFNs). However, there is substantial systemic redundancy in the biological functions of these cytokines [2]. In the vast majority of animal infection models, even when the IL-1β pathway is completely abrogated, whether through targeted pharmacological inhibition with monoclonal antibodies or germline deletion, other pro-inflammatory pathways (e.g., IL-6, IL-18, or type I IFN signaling) may partially compensate for the loss of IL-1β signalling in many infectious settings, although this compensation is pathogen-dependent. This functional division of labor between constitutive defences and inducible responses ensures the continuity of basal immunological competence. See **Figure 1**.

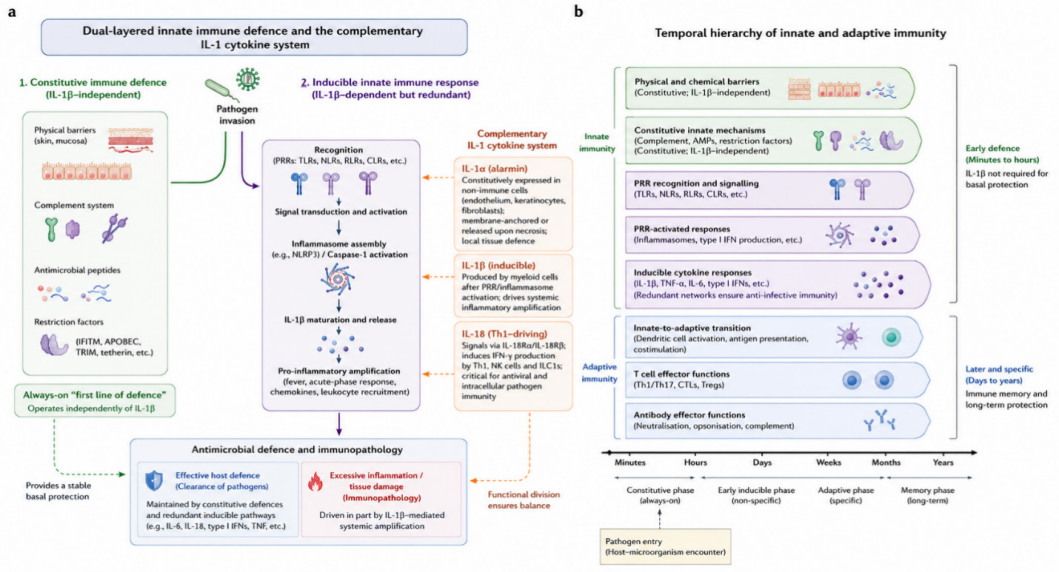

Figure 1. Constitutive innate immunity negatively regulates the inducible immune response.

3. High complementarity of the IL-1 family and the advantages of selective blockade

Although members of the IL-1 family share certain receptors, they exhibit a distinct division of labor regarding cellular sources, expression regulation, and biological functions. IL-1α is constitutively expressed primarily by non-immune cells (such as endothelial cells, keratinocytes, and fibroblasts) and acts as an "alarmin", exerting local tissue defence via membrane anchorage or release upon necrosis. In contrast, IL-1β is primarily induced and synthesized by myeloid cells (monocyte-macrophages and neutrophils) following Toll-like receptor (TLR) or inflammasome activation; after maturation via caspase-1 cleavage, it mediates systemic inflammatory amplification (driving fever, acute-phase responses, and chemokine induction). Furthermore, IL-18 strongly drives IFN-γ production via the IL-18Rα/IL-18Rβ complex, serving as a core factor for type I immune responses mediated by Th1 cells, NK cells, and type 1 innate lymphoid cells (ILC1s), making it indispensable for antiviral and intracellular pathogen defences [3].

This functional complementarity endows the IL-1 system with potent compensatory capabilities. Monoclonal antibodies specifically targeting IL-1β can selectively abrogate pathological systemic inflammatory amplification while fully preserving the local alarmin function of IL-1α and the IFN-γ-inducing activity of IL-18. This avoids the broad immunosuppression that could result from the complete blockade of the IL-1 receptor 1 (IL-1R1). Animal models further corroborate this: while IL-1R1 knockout mice exhibit high susceptibility to a variety of pathogens (including *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Mycobacterium tuberculosis*, and fungi), specific IL-1β deficiency is not lethal [4–6]. In certain infections, the absence of IL-1β can even mitigate infection-associated hyperinflammatory damage [7,8].

4. Pharmacokinetic profiles of biologics and selective distribution to lesions

Under physiological conditions, large-molecule biologics are predominantly confined to the blood circulation and struggle to penetrate the deep interstitial spaces of healthy tissues, thereby minimizing interference with the immune microenvironment of normal tissues. Under inflammatory pathological conditions, however, local vascular permeability increases significantly, allowing monoclonal antibodies to selectively accumulate at the lesion site alongside the exudate. This distribution characteristic of "systemic circulation combined with on-demand local penetration" enables the effective control of systemic inflammation while maximizing the preservation of immune homeostasis in healthy tissues [9,10].

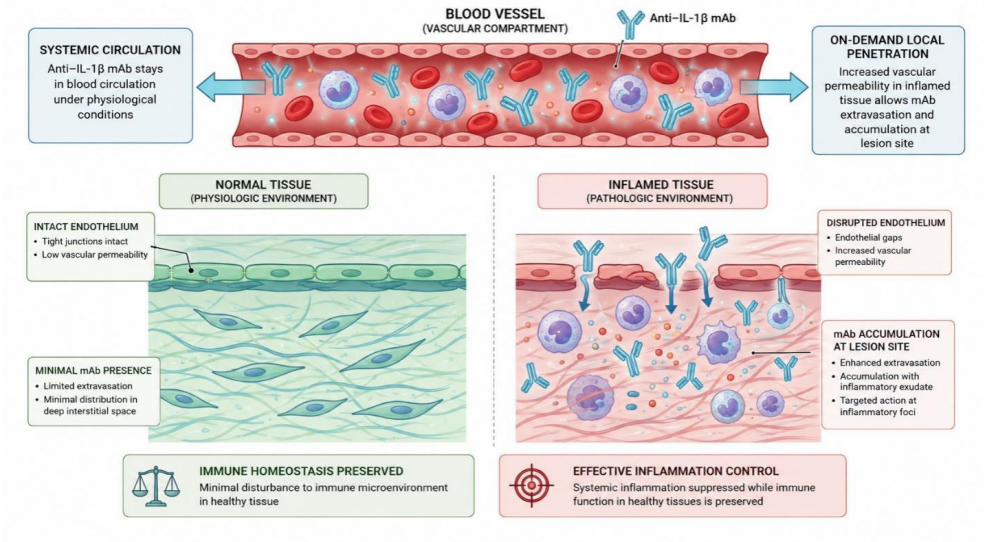

Figure 2. Mechanism of targeted distribution of il-1β monoclonal antibody in normal tissues and inflamed tissues.

5. Precise neutralization of systemic spillover inflammation with preservation of local autocrine/paracrine homeostasis

The secretion of IL-1β relies on unconventional protein secretion (UPS) and bypasses the traditional endoplasmic reticulum-Golgi pathway. This distinct feature dictates its differential behavior under physiological versus pathological conditions. According to studies by Lopez-Castejon et al., IL-1β release exhibits a "continuous spectrum" characteristic that is dependent on stimulus intensity. Under physiological conditions or mild stress, cells utilize a "rescue and redirect" mechanism to release small amounts of IL-1β via macrovesicles or exosomes, thereby mediating local autocrine/paracrine signaling essential for tissue homeostasis and repair [11]. Because monoclonal antibodies are large molecules with limited penetration into healthy tissue interstitial, such low-level, localized physiological communication is generally preserved.

Conversely, in pathological states such as acute gout flares, cardiovascular diseases, or chronic kidney disease, intense inflammatory stimuli trigger pyroptosis. This results in the disruption of cell membrane integrity and the massive "terminal release" of mature IL-1β into the systemic circulation, driving systemic inflammation. In this scenario, mAbs can specifically neutralize this pathological spillover component, achieving precise immunological modulation [12,13].

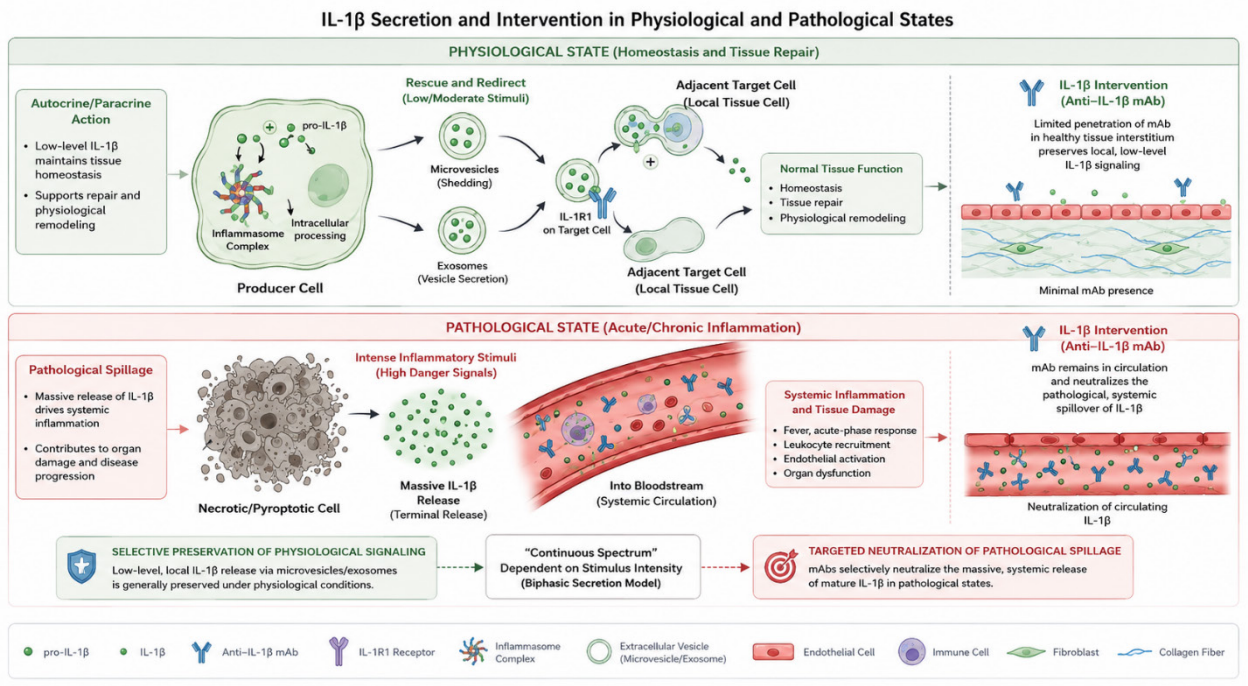

Figure 3. IL-1β secretion and intervention in physiological and pathological states.

6. Evolution of the disease spectrum: IL-1β-mediated sterile inflammation has surpassed infection as the primary challenge to modern health

Over the past two centuries, the burden of human disease has undergone a profound paradigm shift. With advancements in public health, vaccination, and the widespread application of antibiotics, the mortality burden of infectious diseases has declined to approximately 15%. Concurrently, over 80% of deaths in Western societies are now attributed to non-communicable chronic diseases (e.g., cardiovascular disease,

type 2 diabetes, and obesity), which are closely linked to high-calorie "Western diets." Basic research has revealed that Western diets can directly activate the NLRP3 inflammasome, triggering "sterile inflammation" and supplanting traditional pathogens as the primary danger signals recognized by the immune system [14].

Furthermore, Western diets can induce epigenetic reprogramming of bone marrow myeloid progenitors, a process known as trained immunity. IL-1β, released following NLRP3 activation, is the critical mediator driving the formation of this long-term innate immune memory, keeping immune cells in a state of chronic hyperactivation and accelerating immunosenescence. Animal models have confirmed that intervention with IL-1 inhibitors significantly attenuates diet-induced elevations of systemic inflammatory cytokines and acute-phase proteins, highlighting the potential therapeutic value of IL-1β blockade in chronic non-infectious inflammatory diseases [15–17].

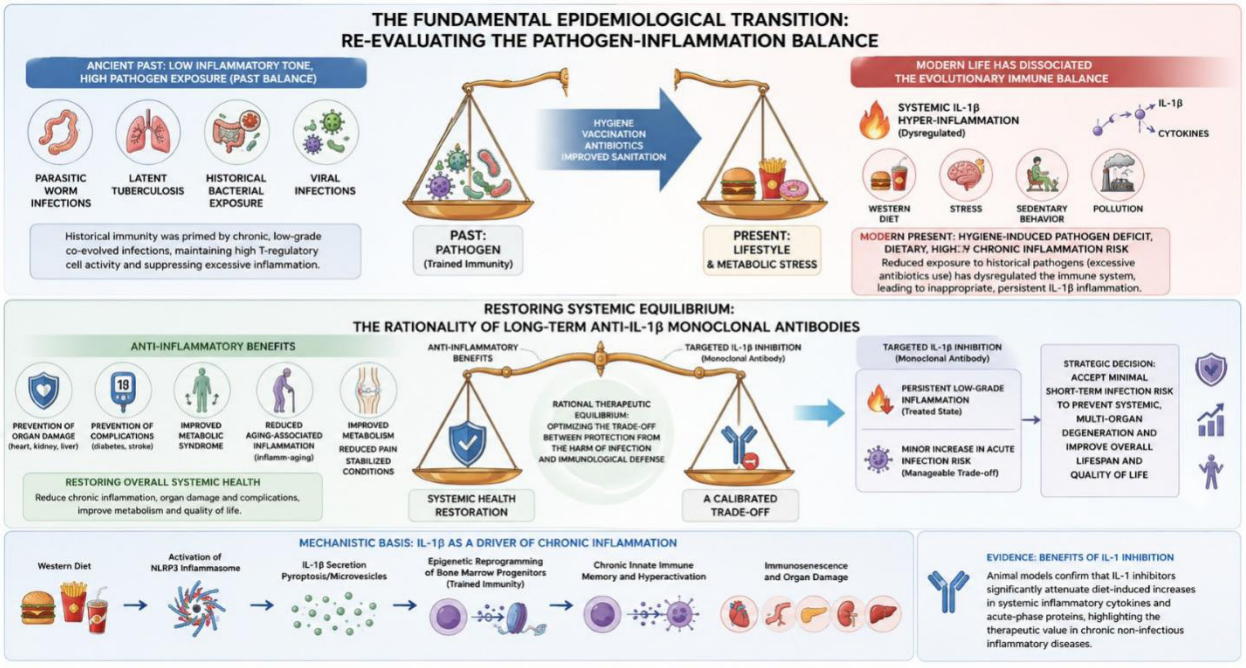

Figure 4. The fundamental epidemiological transition: re-evaluating the pathogen-inflammation balance.

7. Risk assessment for specific pathogen infections and diagnostic interference by IL-1β monoclonal antibodies

Although the overall safety profile of IL-1β mAbs is highly favorable, attention must be directed toward their unique role in defending against specific pathogens. IL-1β can function directly as a "sensor" for microbial proteases: for instance, the SpeB protease secreted by Group A Streptococcus (GAS) can bypass host caspase-1 to directly cleave and activate IL-1β, generating an early, rapid-onset defensive signal. Clinical surveillance indicates a relatively higher proportion of reported invasive GAS infections among patients receiving IL-1β inhibitors, suggesting that blocking this pathway may compromise early, restrictive inflammatory responses to certain bacteria [18]. Group A *Streptococcus* (GAS) remains highly susceptible to standard antibiotics [19]. Clinical evidence from Ridker PM indicates that these infection risks are exceedingly low and do not involve opportunistic pathogens. Furthermore, the risk profile becomes neutral provided that

routine antibiotics are administered promptly for early intervention [20].

Additionally, IL-1β mAbs can suppress infection-associated fever and C-reactive protein (CRP) elevations, leading to the "silencing" of infection symptoms. This necessitates enhanced aetiological monitoring by clinicians, particularly in cases of skin and soft tissue infections, rather than relying solely on fever or CRP metrics for diagnosis [19]. Existing genetic polymorphism studies have not established a strong association between IL-1β loci and the risk of common bacterial or fungal infections. However, given its physiological function as a sensor, appropriate vigilance should be maintained during therapy to optimally balance anti-inflammatory benefits against the potential risk of specific infections [21].

Disclosure statement

The authors declare no conflict of interest.

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