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Hidden Inflammation: Pathophysiological Mechanisms, Clinical Implications, and Diagnostic Considerations—A Review

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I. Abstract

Inflammation is a part of the protective response of the body, however; it does not always manifest in an acute or obvious sense. In others immune activation may be chronic but subclinical. This state, sometimes called silent or low-grade inflammation, may be influencing your health over time. The inflammatory passion is not so violent, but still lasting and ever-burning is the metabolic equilibrium of body functions, vascular tone and cellular homeostasis. Low-level inflammation can be influenced by aging, obesity, metabolic stress and alterations in gut microbiota. These states can trigger natural immune-mediated pathways such as NF-κB signalling and inflammasome activation, resulting in a persistent release of pro-inflammatory molecules. Chronic exposure to this level of immune activation could also promote the onset or progression of chronic diseases – cardiovascular disease, T2D, cancer and neurodegenerative disorders. lignment=justify>One of the major challenges in the treatment of occult inflammation, has been that there have not specific diagnostic criteria. Conventional biomarkers such as C-reactive protein and interleukin-6 may act as surrogates of the burden of inflammation, but they fail to fully account for the intricacy of this aspect. Treatment primarily centres around lifestyle interventions, comprising of a balanced diet, exercise and maintaining an ideal body weight. In this way, subclinical inflammation could be a silent biological status that predisposes some individuals to chronic diseases. Additional study is required to enhance diagnosis and clarify its long-term clinical relevance.

Keywords: *Hidden inflammation; Low-grade inflammation; Chronic inflammation; NF-κB; C-reactive protein; Systemic inflammatory response*

I. Introduction

Inflammation is an inherent defense mechanism of the body against infection, injury, or damaging agents [1]. An acute inflammatory response is generally short-lived, and serves as an overall benefit. It is typically identified by classical findings of redness, swelling, pain and occasionally fever. Once the trigger is eliminated, inflammation usually abates and tissue homeostasis returns [2]. But not all inflammation is obvious or sudden. In many people, the immune system can stay slightly turned on for extended periods without obvious symptoms. This state is sometimes referred to as low-grade, chronic, or subclinical inflammation [3]. For the purposes of this review, we refer to such subclinical inflammation as 'hidden inflammation', and we propose that it may still predispose to chronic disease over time. Unlike acute inflammation, chronic inflammation is not readily apparent. Patients may lack pain, fever or clear infection, but serological markers such as C-reactive protein (CRP), interleukin-6 (IL-6) or tumour

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necrosis factor-alpha (TNF-α) may be mildly increased [4]. These differences may be small and escape clinical detection. However, persistent subclinical immune activation may slowly perturb metabolic control, vasculature function, and cellular homeostasis over time [5]. Data indicate that occult inflammation is involved in the onset and progression of a number of chronic diseases, cardiovascular disease, type 2 diabetes, obesity, neurodegenerative disorders and some types of cancer [6, 7]. It may not cause these conditions per se, but it induces a biological environment conducive to tissue destruction and disease progression. There are several potential reasons that could account for this continued inflammation. Ageing is consistently associated with chronic inflammation profile, in some cases referred to as "inflammaging" [8]. Metabolic abnormalities, including obesity and insulin resistance, are implicated in chronic immune activation partly through inflammation of the adipose tissue [5, 9]. Moreover, changes in the gut microbiota and increased intestinal permeability may permit microbial products to enter blood stream and activate immune pathways [10]. Since latent inflammation prospers subclinically and progresses slowly, its symptoms are not obvious and it never easy to be diagnosed in time. No single biomarker has been able to consistently describe this state, and markers that are often used such as CRP may not fully capture an individual's chronic low-grade inflammatory load [11]. This makes the diagnosis as well as the monitoring rather more difficult. This review attempts to elucidate the biological nature of such hidden inflammation, provide an overview of potential triggers, and do a recapitulation regarding its role in chronic diseases. We also address current detection limitations, the necessity of improved strategies for identifying and treating this quiescent inflammatory state.

Pathophysiology and Mechanisms of Hidden Inflammation

Invisible or silent inflammation also progresses slowly and often silently, without obvious infection or trauma. It's mostly associated for chronic bodily stressors like ageing, obesity or metabolic derangement [3, 5]. In this state, the immune system is kept slightly activated for longer durations. IMMUNE ACTIVATION PATHWAYS One of the primary activators are endogenic danger signals, called DAMPs (Damage-associated molecular patterns). In certain scenarios, the bacterial products of the luminal intestinal contents are available in the circulation to activate immune receptors like TLRs [10]. This activation helps snowball the inflammation within those immune cells. One of the central pathways implicated is nuclear factor kappa-B (NF-κB) which mediates secretion of cytokines including interleukin 6 (IL-6) and tumour necrosis factor alpha (TNF-α) [10]. Even though low, activation appears to be continuous over time and it may cumulatively interfere with tissue properties. The NLRP3 inflammasome is also crucial. It activates the production of (IL-1β) and IL-18 by metabolic and oxidative stress [6, 12]. Sustained activation of this cascade is linked to metabolic and vascular diseases. Oxidative stress is also implicated through the generation of reactive oxygen species (ROS) that cause cellular damage and further promote inflammatory signalling [13]. Furthermore, ageing is associated with the senescence-induced accumulation of cells releasing inflammatory mediators, termed SADS (senescent-associated secretory phenotype) [13]. Adipose tissue in particular, and more so when obese, represents additional key source of low-grade inflammatory cytokines [6]. In general, occult inflammation is generated as a consequence of the interplay between immune receptor activation, inflammasome function, oxidative stress, metabolic dysregulation and ageing [8, 14]. Even though the inflammatory signals are mild, their persistence over time may contribute to chronic disease development. The main mechanisms are summarised in Figure 1.

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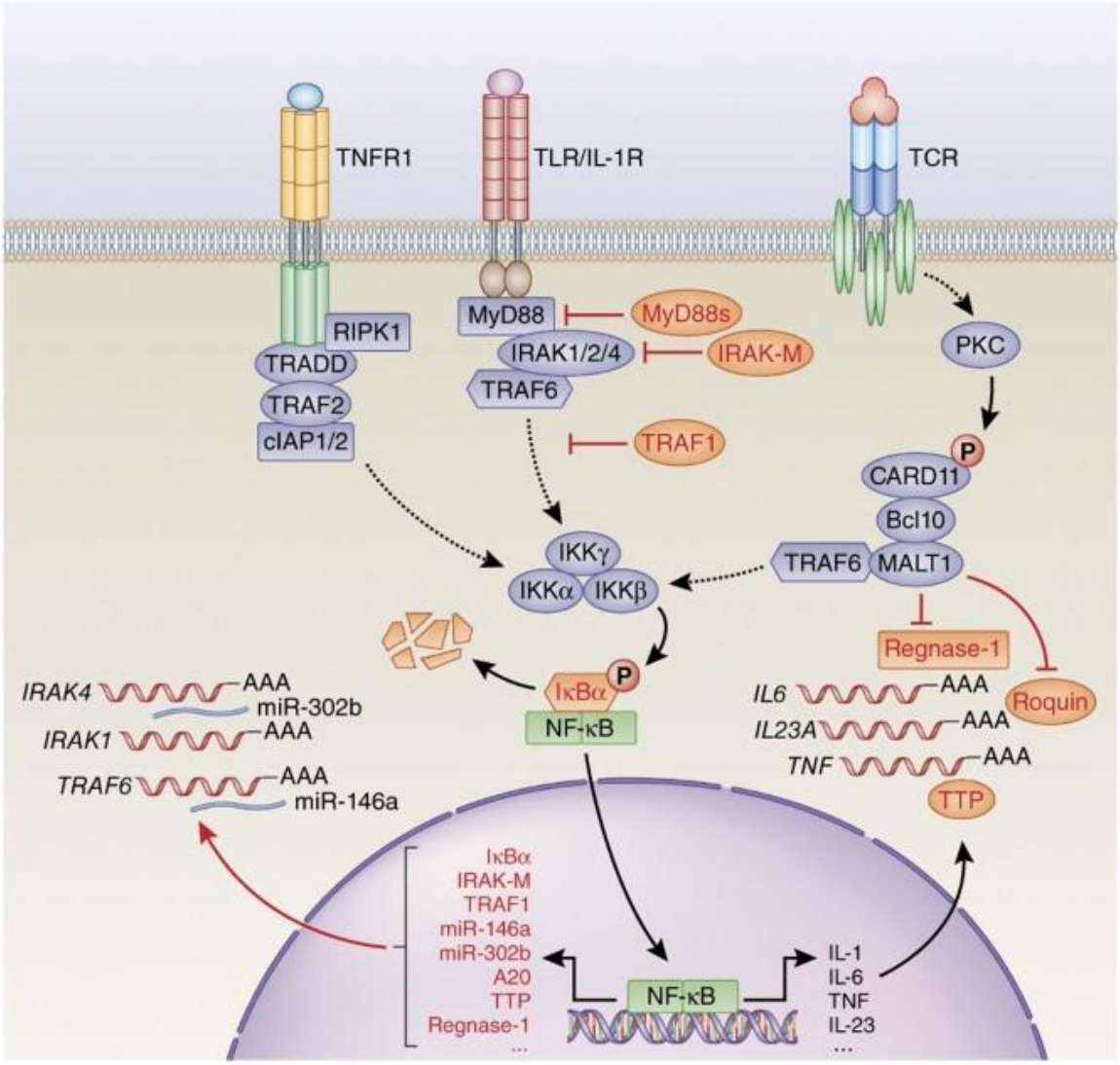

Figure 1 shows a simplified overview of the NF-κB signalling pathway. Activation of receptors such as TNFR1 and Toll-like receptors leads to intracellular signalling through adaptor proteins including MyD88 and TRAF6. This signalling activates the IKK complex, which allows NF-κB to enter the nucleus and stimulate the expression of inflammatory cytokines such as IL-6, TNF and IL-1β. When this pathway remains mildly active for long periods, it may contribute to hidden or low-grade inflammation. Adapted from Afonina IS et al., *Nature Immunology*. 2017;18:861–869.

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Clinical Impact of Hidden Inflammation

Hidden inflammation usually does not cause clear symptoms, but it may slowly influence health over time [3]. Because the immune activity remains mild, many people may not realise it is present. Still, long-term low-grade inflammation can disturb normal tissue function. In obesity and type 2 diabetes, adipose tissue often shows persistent mild inflammation. Fat cells and immune cells release cytokines such as IL-6 and TNF-α, which may interfere with insulin action [15, 16]. This process might contribute to insulin resistance. In cardiovascular disease, chronic inflammation is thought to affect the blood vessel lining and may support plaque formation [17]. Higher levels of C-reactive protein (CRP) have been associated with increased cardiovascular risk, even when there is no obvious infection [18]. There is also evidence suggesting that long-term inflammation may create conditions that favour tumour development [19]. In the brain, mild but persistent inflammation has been linked to neurodegenerative disorders such as Alzheimer's disease [19]. Overall, hidden inflammation may not directly cause disease, but it could act as a background factor that increases susceptibility over time [20]. . The main impacts are summarised in Figure 2.

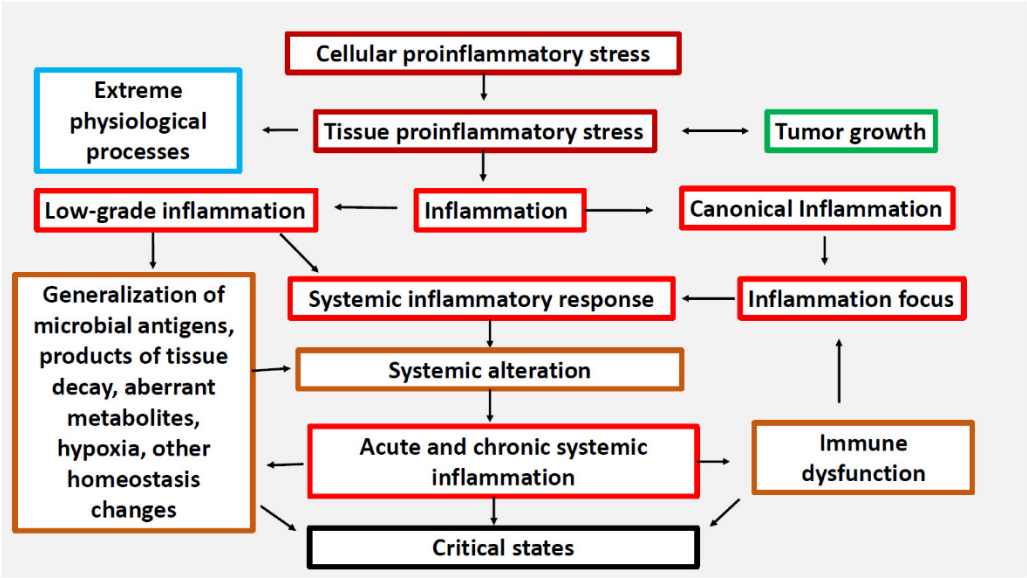

Figure 2. Conceptual progression from low-grade inflammation to systemic inflammatory states. Low-grade inflammation may contribute to systemic inflammatory responses and immune dysfunction. Persistent inflammatory activity can lead to broader systemic alterations and may influence disease progression. Adapted from Zotova N. et al., *International Journal of Molecular Sciences*. 2023;24:1144.

Diagnostic Challenges and Biomarkers

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Detecting hidden inflammation is not always easy. Because the inflammatory activity is mild, routine clinical tests may not clearly show it [21]. There is still no single marker that can fully define low-grade inflammation. C-reactive protein (CRP), especially high-sensitivity CRP (hsCRP), is commonly used in clinical practice. It may reflect systemic inflammation, but it can also increase during acute infections or other conditions [22]. For this reason, CRP alone may not always give a complete picture of chronic low-grade inflammation. Cytokines such as interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α) are also used in research settings. However, their levels can fluctuate, and measurement methods are not always standardised [11]. This makes interpretation sometimes difficult. Recently, some studies have suggested that combining multiple biomarkers may provide a better estimate of inflammatory burden [23]. Advances in molecular techniques, including high-sensitivity assays and multi-omics approaches, may also help improve detection in the future. Overall, more work is still needed to define clear diagnostic criteria for hidden inflammation. At present, assessment often depends on a combination of laboratory markers and clinical context.

Prevention and Management of Hidden Inflammation

While hidden inflammation can build gradually, certain lifestyle changes could help mitigate its intensity. These strategies are not immune indifferentiation therapies, however they could help maintain general immune balance. Diet may be a significant factor as well. Some studies have reported lower inflammatory markers in individuals with diets high in fruits, vegetables, whole grains and omega-3 fatty acids [24, 25]. Conversely, detractors of processed foods and sugar intake can possibly accelerate inflammation. Exercise can also make a volume of difference. Mild activity can decrease inflammatory markers, improve glucose and lipid metabolism [26]. It usually takes some time for the effect to kick in and consistency is key. Adjutant 2: Sufficient rest, along with stress management, may also impact immune regulation. In some studies, chronically stressed and sleep-deprived people were found to have increased inflammatory markers [3]. In some clinical contexts, anti-inflammatory drugs or biological agents are prescribed, particularly for cardiovascular or autoimmune diseases [27]. These are not, however, protocols that specifically target occulted inflammation alone. In general, treating silent inflammation involves lifestyle strategies to promote health and medications to manage underlying diseases. Further studies are necessary to determine precise treatment recommendations.

Conclusion

Silent inflammation is a state of continued low-grade immune activation, emerging in the absence of apparent clinical disease. Unlike acute inflammation, it generally does not accompany with the classical findings like fever, erythema and pain that cause late detection. However, the picture has become more complex and data are mounting that increased low-grade inflammatory activity is promoting chronic tissue disruption to homeostasis and heightened risk of a variety of other diseases. There seems to be more than one factor in the formation of this inflammatory condition. Ageing, metabolic dysfunction, adipose and gut microbiota changes have all been proposed to be contributing factors. These factors could potentially coalesce on innate immune signal transduction pathways, resulting in steady but low levels of pro-inflammatory mediator generation. The degree of the inflammatory reaction is minimal, but chronic in nature may have compounded biologic influences. The main drawback of this field is the lack of an universally agreed definition and validated diagnostic criteria. By far the most widely used are circulating biomarkers such as high-sensitivity c-reactive protein (hs-CRP) and interleukin-6 (IL-6), however these

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only provide a partial view of the complex environment. Novel experimental techniques, such as multi-biomarker profiling and advanced molecular methods could provide better characterisation; their adaptation into standard clinical practice is limited though. From a translation perspective, existing intervention approaches focus predominantly on lifestyle-based interventions. Compliance with healthy diet patterns, physical activity, adequate sleep and body weight can decrease inflammation and help to maintain optimal metabolic and immune balance. While these are not therapies directed specifically at subclinical inflammation itself, they represent accessible and evidence-based strategies to reduce these risks. In conclusion, occult inflammation cannot be considered as a single disease but as part of the spectrum of immune dysregulation. It may be the foundational biological substance that triggers or exacerbates multiple chronic diseases. More mechanistic studies and methodological improvements are needed for clarification of terms, to improve the detection capabilities, and to estimate potential influences on therapeutic strategies.

Declarations

Ethics Approval and Consent to Participate

This study is a narrative review article and does not involve human participants, animal experiments, or clinical trials. Therefore, ethical approval and informed consent were not required.

Consent for Publication

Not applicable.

Availability of Data and Materials

All data discussed in this review are derived from previously published studies, which are properly cited in the reference list.

Competing Interests

The authors declare that they have no competing interests.

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Authors' Contributions

Ali Mohammed Sameen contributed to the conceptualisation, literature review, and manuscript drafting. Ibraheem Abdulnabi Shabeeb contributed to literature analysis and manuscript revision. Ahmed J. Alfahdawi contributed to critical revision and final approval of the manuscript. All authors read and approved the final manuscript.

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