CD16+ Monocytes in Thrombotic and Cardiovascular Diseases: A Survey

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Abstract

CD16+ monocytes, marked by the Fc gamma receptor III (CD16), play a pivotal role in thrombotic and cardiovascular diseases through their contributions to inflammation, immune response, and coagulation processes. This survey provides a comprehensive examination of CD16+ monocytes, highlighting their classification into classical, intermediate, and non-classical subsets, each with distinct functional roles in immunity and inflammation. The dynamics of these monocyte subsets are critical in both acute and chronic inflammatory responses, influencing the pathogenesis of thrombotic diseases such as atherosclerosis. CD16+ monocytes interact with platelets and coagulation pathways, contributing to thrombotic risk, particularly in inflammatory conditions like COVID-19. Technological advancements, such as single-cell RNA sequencing and microrheology, have enhanced our understanding of monocyte heterogeneity and their interactions with coagulation systems, offering potential diagnostic and therapeutic applications. Despite significant progress, gaps remain in standardizing methodologies and elucidating the precise mechanisms of monocyte function. Future research should focus on these areas, aiming to develop targeted therapies that modulate monocyte activity and improve clinical outcomes in cardiovascular diseases. Understanding the immunometabolic interface and its impact on cardiovascular risk is also crucial, as it highlights the complex interplay between metabolic and immune pathways. Overall, this survey underscores the critical role of CD16+ monocytes in thrombotic and cardiovascular diseases, advocating for continued research and technological integration to enhance patient care.

1 Introduction

1.1 Structure of the Survey

This survey provides a thorough examination of CD16+ monocytes and their roles in thrombotic and cardiovascular diseases. It begins with an introduction that underscores the relevance of CD16+ monocytes in inflammation and immune responses, setting the context for the subsequent detailed analysis. The initial section, Background and Definitions, establishes foundational knowledge by defining essential terms and concepts, followed by a discussion on the characteristics, classification, and functional heterogeneity of CD16+ monocytes.

Subsequent sections explore the specific contributions of CD16+ monocytes to inflammation and immune responses. The section on the Role of CD16+ Monocytes in Inflammation assesses their involvement in inflammatory processes, including monocyte subset dynamics, signaling pathways, and interactions with other immune cells. The CD16+ Monocytes and Immune Response section focuses on pathogen recognition, cytokine production, and the functional diversity of monocyte subsets, culminating in a discussion of immune memory.

The survey then addresses the Impact on Coagulation Processes, analyzing how CD16+ monocytes influence coagulation through pathway activation, subset interactions, and advancements in

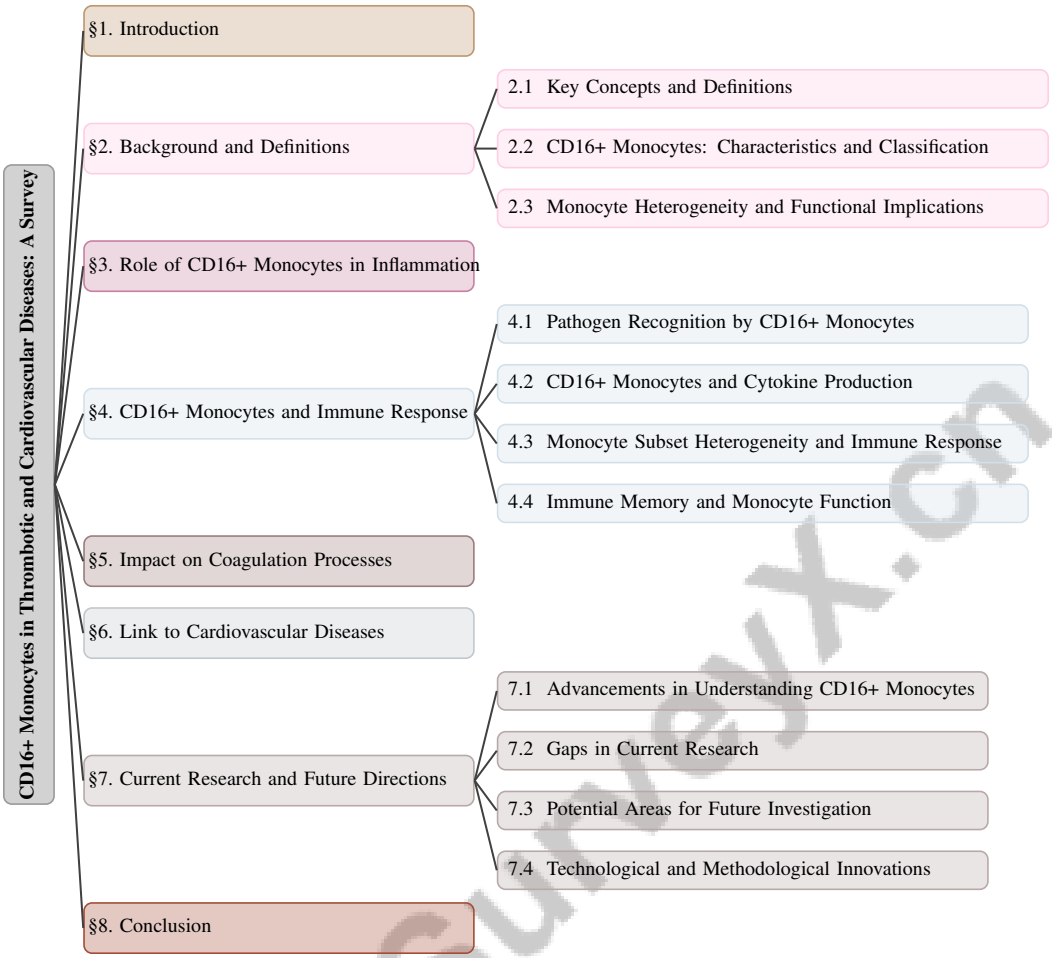

Figure 1: chapter structure

measurement technologies. This is followed by a section connecting CD16+ monocytes to cardiovascular diseases, which examines pathophysiological mechanisms, the role of inflammation, and the immunometabolic interface associated with cardiovascular risk.

The penultimate section, Current Research and Future Directions, reviews recent findings, identifies research gaps, and proposes areas for future investigation, highlighting technological and methodological innovations. The survey concludes by summarizing key insights and emphasizing the clinical and research significance of CD16+ monocytes in the context of thrombotic and cardiovascular diseases.The following sections are organized as shown in Figure 1.

2 Background and Definitions

2.1 Key Concepts and Definitions

CD16+ monocytes, defined by the Fc gamma receptor III (CD16) expression, are pivotal in immune responses and the development of thrombotic and cardiovascular diseases [1, 2]. These cells are major producers of inflammatory mediators, influencing both acute and chronic inflammation, making them promising targets for anti-inflammatory therapies. Thrombotic diseases, such as venous thromboembolism and coronary atherosclerosis, involve obstructive blood clot formation, posing significant health risks.

Cardiovascular diseases, encompassing disorders affecting the heart and blood vessels, are often exacerbated by factors like hypertension, hyperlipidemia, and inflammation [3]. Inflammation, a crucial immune defense component, recruits and activates immune cells to fight pathogens and facilitate

tissue repair, but chronic inflammation can impair cardiac function and accelerate cardiovascular disease progression [4]. The administration of endotoxins in research highlights the complexity of inflammation's effects on immune function [5].

Coagulation, essential for preventing excessive bleeding, involves the conversion of fibrinogen to fibrin to stabilize clots. Dysregulation in this process can lead to thrombotic events, underscoring the need to understand immune cell interactions with coagulation pathways [6]. CD16+ monocytes are integral to thrombotic and cardiovascular disease pathophysiology, highlighting their clinical importance. Their differentiation into macrophages and dendritic cells in vivo illustrates their diverse roles in inflammatory diseases [7]. The survey categorizes immune responses into innate and adaptive immunity, elucidating their roles in stroke phases [8], and introduces pathways such as NF-B, MAPK, and JAK-STAT, crucial in regulating the inflammatory response [9]. Additionally, CD16+ monocytes are pivotal in inflammation and immune responses, akin to biochemical pathways that enhance gene dependency inference [10].

2.2 CD16+ Monocytes: Characteristics and Classification

CD16+ monocytes, a distinct subset of human monocytes, are identifiable by the CD16 surface marker and traditionally classified into three phenotypic subsets: classical (CD14++CD16-), intermediate (CD14++CD16+), and non-classical (CD14+CD16++). This classification highlights the functional diversity within the monocyte population, with non-classical monocytes exhibiting pronounced pro-inflammatory properties and potential senescence-related characteristics, while the intermediate subset shows varying functional responses based on environmental conditions. Advances in single-cell transcriptomics and mass cytometry have refined our understanding of these subsets, revealing their roles in chronic inflammatory diseases and age-related immune alterations [1, 11, 12, 13, 14].

Classical monocytes, with high CD14 and no CD16, are essential in initial immune responses, demonstrating robust phagocytic activity and cytokine production, crucial for pathogen clearance and acute inflammation [15]. Intermediate monocytes, expressing both CD14 and CD16, serve as a transitional population important in antigen presentation and are associated with inflammatory responses across various diseases [13]. Non-classical monocytes patrol the vascular endothelium, implicated in tissue repair and inflammation resolution, and exhibit a pro-inflammatory phenotype linked to chronic inflammatory conditions, interacting with activated platelets to modulate immune responses. Their adaptability to physiological and pathological conditions further emphasizes the dynamic nature of monocyte subsets [16].

Recent research proposes a novel five-marker combination for objectively delineating monocyte subsets, addressing limitations of traditional CD16–CD14 classifications due to subjectivity and variability [11]. This approach enhances the assessment of monocyte subset perturbations during infections and other pathological states, with a focus on absolute cell counts rather than percentages, offering a more reliable prognostic tool [17].

Understanding the characteristics and classification of CD16+ monocytes is crucial for elucidating their roles in health and disease, particularly concerning thrombotic and cardiovascular diseases. This knowledge aids in developing targeted therapeutic strategies that specifically modulate the activity of distinct monocyte subsets—classical, intermediate, and non-classical—thereby improving patient outcomes in various chronic inflammatory diseases by leveraging their unique functional properties and roles in disease progression [11, 14, 1, 7].

2.3 Monocyte Heterogeneity and Functional Implications

Monocyte heterogeneity is a critical aspect of the immune system, characterized by distinct subsets with specialized functions that adapt to varying physiological and pathological conditions. The complexity of monocyte biology is highlighted by their diverse differentiation pathways and functional roles, significantly contributing to disease processes [1]. The classical (CD14++CD16-), intermediate (CD14++CD16+), and non-classical (CD14+CD16++) monocyte subsets exhibit unique phenotypic and functional characteristics essential for comprehending their roles in health and disease.

The intermediate monocyte subset has garnered considerable attention due to conflicting reports regarding its functional characteristics. It is associated with both pro-inflammatory and anti-inflammatory responses, reflecting its dual role in immune regulation [14]. The functional plas-

ticity of intermediate monocytes is further influenced by factors such as aging, which affects their transcriptional responses and functionality within the innate immune system [13].

Activated platelets significantly modulate monocyte function, particularly by inducing CD16 expression on classical CD14+ monocytes. This interaction is vital for understanding the mechanisms underlying inflammatory responses and the transition of monocyte subsets during immune activation [18]. The heterogeneity of monocytes extends to their roles in inflammation and cancer, where they exhibit varying functions essential for disease progression and therapeutic interventions [19].

In conditions such as sepsis, monocyte subpopulations orchestrate the immune response, yet the implications of their absolute counts for patient outcomes remain underexplored [16]. Altered distributions of monocyte subsets have been documented in various diseases, including giant cell arteritis (GCA) and polymyalgia rheumatica (PMR), characterized by a significant increase in classical monocytes and a relative decrease in non-classical monocytes [20]. In chronic lymphocytic leukemia (CLL) patients, an increased percentage of intermediate and non-classical monocytes compared to controls suggests their potential as biomarkers for disease states [21].

The observed complexity and heterogeneity among monocyte subsets, characterized by distinct phenotypic and functional properties, underscore the critical need for an in-depth understanding of their diverse roles in immune regulation and the pathogenesis of various diseases. Emerging research indicates that these subsets exhibit unique developmental pathways and responses to environmental stimuli that influence their contributions to both homeostasis and disease states [22, 19, 14]. This knowledge is essential for developing targeted therapeutic strategies to modulate monocyte activity and improve clinical outcomes.

In recent years, understanding the role of CD16+ monocytes in inflammation has become increasingly important in immunological research. These monocytes are not merely passive participants; they actively engage in various immune responses through complex interactions with other immune cells. To elucidate this dynamic, Figure 2 illustrates the hierarchical structure of the role of CD16+ monocytes in inflammation. This figure details the dynamics of monocyte subsets, key signaling pathways, and their interactions with T lymphocytes, dendritic cells, and neutrophils. Furthermore, it highlights the classification of monocyte subsets and emphasizes the significance of CD16+ monocytes as potential therapeutic targets in modulating immune responses. By presenting this information visually, the figure enhances our understanding of the intricate network of immune interactions and the pivotal role that CD16+ monocytes play in inflammation.

3 Role of CD16+ Monocytes in Inflammation

3.1 Monocyte Subset Dynamics and Inflammation

Monocyte subsets, defined as classical (CD14++CD16), intermediate (CD14++CD16+), and non-classical (CD14+CD16++), play pivotal roles in inflammatory responses, each characterized by distinct gene expression profiles and functional roles. Non-classical monocytes are notably pro-inflammatory, particularly upon Toll-like receptor (TLR) stimulation, and their accumulation in older adults is associated with chronic inflammatory conditions like atherosclerosis and osteoarthritis, presenting potential therapeutic targets [11, 12, 1]. In contrast, classical monocytes initiate immune responses, while intermediate and non-classical subsets are more involved in chronic inflammation and tissue repair.

In severe conditions such as sepsis, monocyte dynamics shift from CD16 to CD16+ pro-inflammatory monocytes, reflecting a transition to hyperinflammation and subsequent immune suppression [23, 16]. Variations in surface markers like CD163 and HLA-DR among monocyte subpopulations further influence their inflammatory roles, as observed in chronic lymphocytic leukemia (CLL) [21]. A refined classification using a five-marker gating strategy (CD33, CD86, CD64, HLA-DR, and CCR2) enhances understanding of monocyte perturbations during inflammation [11]. Research focuses on mechanisms of inflammatory response, organ-specific reactions, and inflammation resolution, based on stimuli type and affected organs [9].

Comprehending monocyte subset dynamics is crucial for developing targeted therapeutic strategies to modulate their activity, especially in managing inflammation and improving clinical outcomes. Advances in gene expression analysis have illuminated phenotypic and functional differences among these subsets, presenting new opportunities for tailored interventions in inflammatory diseases

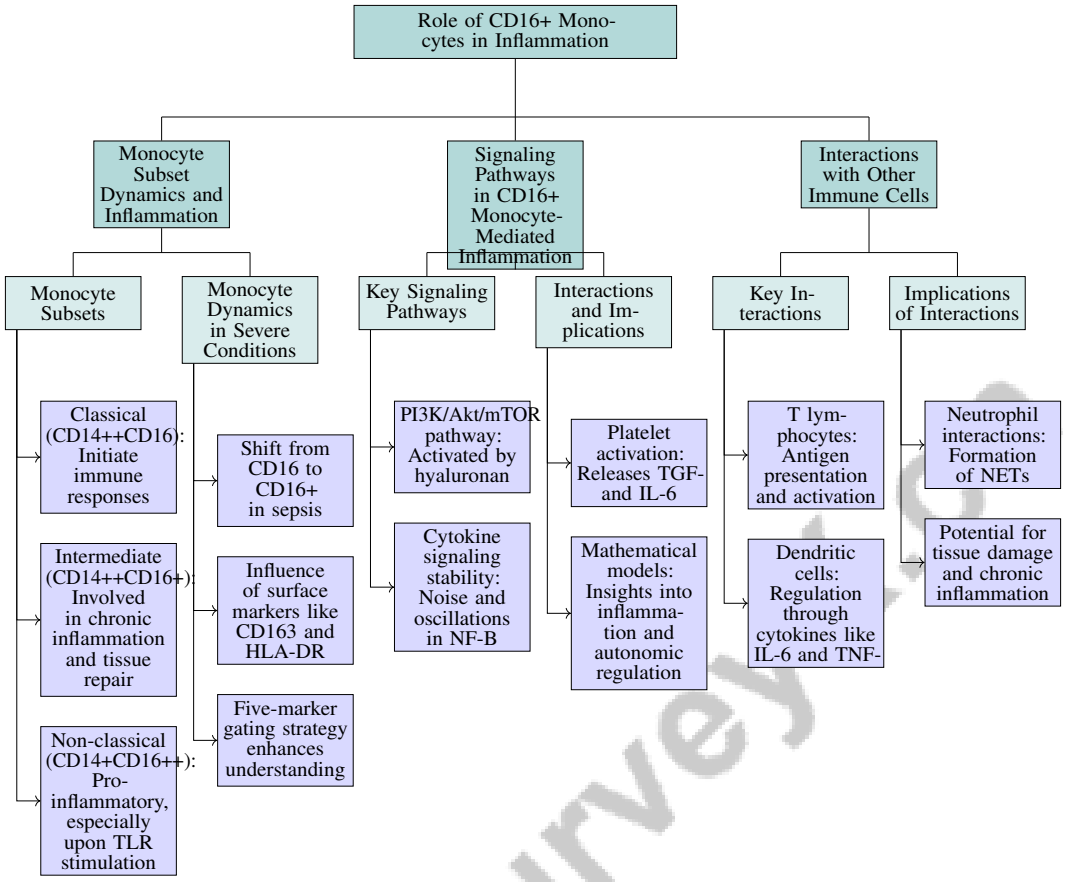

Figure 2: This figure illustrates the hierarchical structure of the role of CD16+ monocytes in inflammation, detailing monocyte subset dynamics, key signaling pathways, and interactions with other immune cells. It highlights the classification of monocyte subsets, the signaling pathways involved in CD16+ monocyte-mediated inflammation, and their interactions with T lymphocytes, dendritic cells, and neutrophils, emphasizing their role in immune responses and potential therapeutic targets.

[14, 17]. The dual role of immune responses, where initial activation can lead to further tissue injury, presents challenges in harnessing these responses for therapeutic protection.

3.2 Signaling Pathways in CD16+ Monocyte-Mediated Inflammation

The signaling pathways governing CD16+ monocyte-mediated inflammation are complex and pivotal in modulating immune responses. As illustrated in Figure 3, this figure shows the hierarchical structure of signaling pathways involved in CD16+ monocyte-mediated inflammation, highlighting the roles of the PI3K/Akt/mTOR pathway, platelet activation, and cytokine signaling in modulating immune responses. The PI3K/Akt/mTOR pathway, activated by hyaluronan, is critical in driving inflammation in CD16+ monocytes, influencing cellular survival, proliferation, and differentiation [15]. Platelet activation releases cytokines such as TGF- and IL-6, modulating monocyte function and promoting differentiation into pro-inflammatory phenotypes [18]. These interactions underscore the intricate signaling networks regulating monocyte activity and highlight the significant role of platelet-derived factors in enhancing inflammation.

Cytokine signaling stability is influenced by noise and lower secondary amplitude oscillations, as evidenced in NF-B signaling models, ensuring sustained inflammatory responses [24]. Mathematical models integrating physiological responses offer insights into the interplay between inflammation and autonomic regulation, particularly following endotoxin administration [25, 5]. Despite these advancements, current studies often fail to fully elucidate the functional implications of monocyte

heterogeneity and the specific pathways leading to different subset production [22]. Addressing these gaps is vital for understanding CD16+ monocyte contributions to inflammation and developing targeted therapeutic strategies.

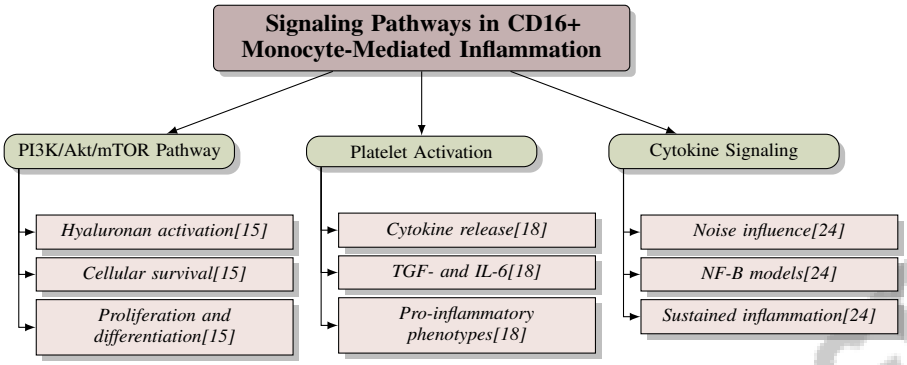

Figure 3: This figure shows the hierarchical structure of signaling pathways involved in CD16+ monocyte-mediated inflammation, highlighting the roles of the PI3K/Akt/mTOR pathway, platelet activation, and cytokine signaling in modulating immune responses.

3.3 Interactions with Other Immune Cells

CD16+ monocytes orchestrate immune responses through interactions with various immune cells, significantly influencing inflammation and the progression of thrombotic and cardiovascular diseases. These interactions, mediated by specific surface receptors and cytokine secretion, modulate lymphocyte, dendritic cell, and neutrophil activity, essential for antigen presentation and inflammation [26, 2, 13, 14, 8].

Key interactions involve CD16+ monocytes and T lymphocytes, where monocytes present antigens to T cells, enhancing activation and proliferation, augmented by co-stimulatory molecules like CD86 and HLA-DR [14]. CD16+ monocytes also interact with dendritic cells, regulating immune responses through cytokines like IL-6 and TNF-, enhancing dendritic cell antigen-presenting capability [18]. Neutrophil interactions involve the formation of neutrophil extracellular traps (NETs), influenced by monocyte-derived cytokines and reactive oxygen species (ROS) [15]. While essential for pathogen clearance, these interactions may contribute to tissue damage and chronic inflammation when dysregulated [16].

The interactions of CD16+ monocytes with various immune cells are vital in modulating immune responses, revealing their intricate role in the immune network dynamics during health and disease. These monocyte subsets, defined by distinct surface markers and functional characteristics, are essential for understanding immune regulation complexities, particularly in chronic inflammatory diseases and aging, where their functionality may be compromised. Recent advancements in single-cell transcriptomics have further elucidated the heterogeneity of these monocyte populations, highlighting their potential as therapeutic targets in various pathologies, including obesity, atherosclerosis, and neurodegenerative disorders [1, 11, 13, 14, 7]. Understanding these interactions is crucial for developing targeted therapies aimed at modulating monocyte activity to improve outcomes in thrombotic and cardiovascular diseases.

4 CD16+ Monocytes and Immune Response

4.1 Pathogen Recognition by CD16+ Monocytes

CD16+ monocytes are integral to the innate immune response, recognizing pathogens through pattern recognition receptors (PRRs) that detect pathogen-associated molecular patterns (PAMPs). Key receptors, including Toll-like receptors (TLRs) and C-type lectin receptors (CLRs), trigger signaling cascades activating nuclear factor kappa B (NF-B) and inducing pro-inflammatory cytokine production [26]. The expression of chemokine receptors on monocyte subsets dictates their migration, enabling CD16+ monocytes to home to infection sites, engage pathogens, and present antigens to T

cells [20]. This antigen presentation bridges innate and adaptive immunity, with CD16+ monocytes retaining antigen memory, thereby enhancing T cell activation compared to newly challenged antigen-presenting cells (APCs) [26].

As illustrated in Figure 4, the role of CD16+ monocytes in immune responses encompasses crucial processes such as pathogen recognition and antigen presentation, while also offering therapeutic insights for managing infectious diseases. Understanding these interactions, especially in human macrophages, is critical for designing therapies that enhance pathogen recognition and improve outcomes in infectious and inflammatory diseases. Insights from protein-protein interaction networks can guide therapeutic strategies to modulate inflammatory responses and promote tissue healing in infections like Mycobacterium tuberculosis or SARS-CoV-2 [2, 27, 28, 9].

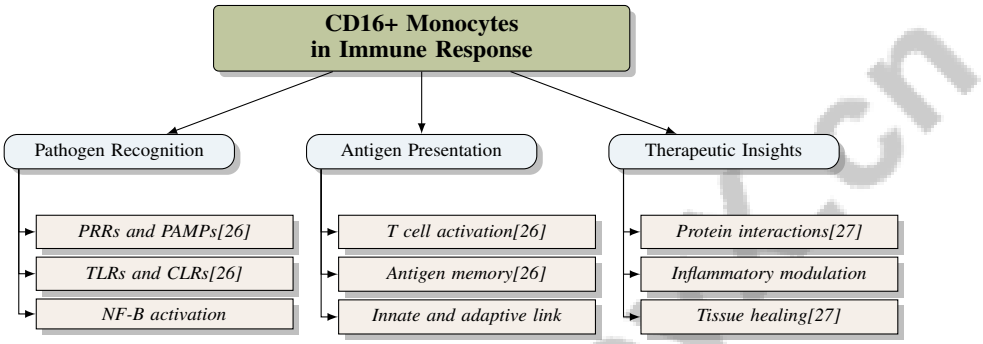

Figure 4: This figure illustrates the role of CD16+ monocytes in immune responses, highlighting pathogen recognition, antigen presentation, and therapeutic insights for infectious diseases.

4.2 CD16+ Monocytes and Cytokine Production

CD16+ monocytes play a crucial role in cytokine production, affecting inflammation and metabolic health. Upon activation, they produce various cytokines, including interleukin-10 (IL-10) in response to tumor-derived microvesicles, modulating anti-inflammatory responses [15]. Factors like aging and the cellular environment influence their cytokine production profile, with aging impairing monocyte immune capabilities and reducing antiviral interferons and pro-inflammatory cytokines [13]. In sepsis, cytokine dynamics in CD16+ monocytes can predict patient survival [16]. CD163 expression, predominant in classical monocytes, indicates anti-inflammatory properties, contrasting with the impaired immune stimulation in non-classical monocytes [21]. This highlights CD16+ monocytes' regulatory role in balancing inflammatory signals. Noisy oscillations in pathways like NF-B may optimize cellular communication and responses to inflammation [24]. Thus, CD16+ monocytes are essential mediators of inflammation and metabolic processes, with therapeutic potential for modulating immune responses [29].

4.3 Monocyte Subset Heterogeneity and Immune Response

Monocyte subset heterogeneity is vital to immune responses, with each subset contributing uniquely to immune functions and disease processes. Classical monocytes are active in early innate immune responses, showing robust phagocytic activity and cytokine production. Non-classical monocytes, with a senescence-associated secretory phenotype (SASP), contribute to chronic inflammation and patrol the endothelium for immune surveillance and tissue repair [12]. Intermediate monocytes exhibit both pro- and anti-inflammatory responses [23]. Recent advancements in subset classification, like a five-marker combination, enhance objectivity and marker stability [11]. This is crucial in diseases like COVID-19, where monocytes impact innate immune response and inflammation [23]. Understanding monocyte heterogeneity is essential for developing targeted therapies, with gene expression analysis revealing significant variations in phenotypic and functional characteristics influenced by origins, developmental pathways, and environmental signals. This knowledge enhances our understanding of monocyte biology and presents opportunities for therapeutic immune modulation in infections, inflammation, and cancer [22, 19, 14].

4.4 Immune Memory and Monocyte Function

The concept of immune memory extends beyond T and B lymphocytes to include innate immune cells like monocytes, macrophages, and dendritic cells, which exhibit a form of "memory" or "training" that enhances responses to previously encountered antigens. Dendritic cells maintain a pro-inflammatory phenotype and elevated immune activation after rest, highlighting their role in immunological memory alongside T and B lymphocytes [26, 30, 8]. Monocytes contribute to "trained immunity," characterized by epigenetic reprogramming and metabolic changes that enhance responsiveness to future challenges. CD16+ monocytes undergo functional reprogramming after specific stimuli exposure, altering cytokine production profiles and enhancing effector functions upon re-stimulation. This supports the notion of innate immune cells exhibiting memory-like properties, leading to more efficient responses than traditional memory in T and B cells [26]. Monocyte involvement in immune memory is particularly relevant in infections and vaccinations, where trained immunity provides enhanced protection against diverse pathogens. Alterations in histone modifications and metabolic pathways, including glycolysis and oxidative phosphorylation, facilitate this response, enabling effective responses to immune challenges, especially with age-related immune function changes [14, 13, 7]. Understanding immune memory mechanisms in monocytes is crucial for developing novel strategies to enhance vaccine efficacy and provide broad-spectrum protection against infectious diseases. Studies indicate long-lasting functional changes in innate immune cells post-pathogen exposure, which could improve vaccine outcomes and defenses against various infectious agents [26, 13, 30, 8]. Elucidating monocytes' role in immune memory may offer insights into inflammatory and autoimmune disease pathogenesis, where dysregulated trained immunity could lead to chronic inflammation and tissue damage.

5 Impact on Coagulation Processes

The interaction between immune responses and coagulation processes, particularly involving CD16+ monocytes, is critical in activating coagulation pathways. These monocytes, through their interactions with platelets, play a significant role in both physiological and pathological coagulation, offering insights into mechanisms that govern coagulation dynamics and thrombotic conditions.

5.1 CD16+ Monocytes and Coagulation Pathway Activation

CD16+ monocytes are central to coagulation pathway activation, closely linked with inflammation and immune responses. Their interaction with activated platelets enhances phagocytic activity and modulates coagulation processes, a relationship notably observed in COVID-19, where coagulopathy is common in severe cases [18, 31]. Monitoring coagulation parameters in such scenarios provides valuable prognostic insights.

The kinetics of coagulation factor generation on CD16+ monocytes' surfaces significantly impact coagulation pathway activation, particularly in fibrin deposition during hemostasis and pathological processes [32]. The mutual influence of platelet and coagulation factor activation during vascular injury is crucial for effective hemostasis [33]. Chronic inflammation's adverse effects on metabolic health necessitate a comprehensive understanding of immune responses and their impact on coagulation [29].

Technological advancements, such as microrheology techniques and stochastic models, have improved our understanding of coagulation's mesoscopic properties, enhancing the analysis of coagulation dynamics [34, 35]. The Bayesian Dependence Modeling method further elucidates CD16+ monocytes' role in activating coagulation pathways [10].

Understanding the distinct functional properties of monocyte subsets, particularly the intermediate subset linked to increased all-cause mortality and heart failure-related hospitalizations, is essential for developing targeted therapeutic strategies to modulate monocyte activity and improve clinical outcomes in thrombotic and cardiovascular diseases [14, 17].

5.2 Monocyte Subsets and Coagulation Dynamics

Monocyte subsets, including classical, intermediate, and non-classical monocytes, uniquely influence coagulation processes, reflecting their distinct functional characteristics. As illustrated in Figure 5,

these subsets play critical roles in coagulation dynamics, with classical monocytes, known for their high phagocytic activity, being essential in the early phases of hemostasis. They interact with activated platelets and coagulation factors to initiate clot formation and maintain vascular integrity [20, 12, 33, 1].

Intermediate monocytes, expressing both CD14 and CD16, amplify coagulation phases, especially in hypercoagulable conditions, where interactions with endothelial cells and platelets may exacerbate thrombotic processes [34]. Their presence is linked to increased thrombin generation, underscoring their role in the coagulation cascade.

Non-classical monocytes, characterized by high CD16 expression, are involved in resolving inflammation and facilitating tissue repair. However, in severe COVID-19, they may contribute to coagulation dysfunction, as evidenced by altered coagulation profiles in affected patients. The interplay between monocyte subsets and coagulation factors is further complicated by the rate-limiting kinetics of coagulation factor generation on cell membranes under flow conditions [32].

Research on SARS-CoV-2's impact on hemostasis reveals significant coagulation parameter alterations in COVID-19 patients, highlighting the critical roles of monocyte subsets in influencing coagulation dynamics. The absolute count of intermediate monocytes is independently associated with increased risks of all-cause mortality and heart failure-related hospitalizations, emphasizing the importance of monitoring these parameters for effective disease management [14, 17].

Understanding the roles of monocyte subsets in coagulation dynamics is crucial for developing targeted therapeutic strategies to modulate monocyte activity and enhance clinical outcomes in thrombotic and cardiovascular diseases. This knowledge elucidates the complex pathophysiological mechanisms underlying coagulation dysfunction in infectious diseases, particularly COVID-19, where endothelial dysfunction, altered blood flow, and platelet activation contribute to a prothrombotic state. Insights from this research may identify potential therapeutic targets, including activated protein C and PAI-1 antagonists, offering new intervention avenues and personalized thromboprophylaxis strategies [36, 27, 33, 34, 6].

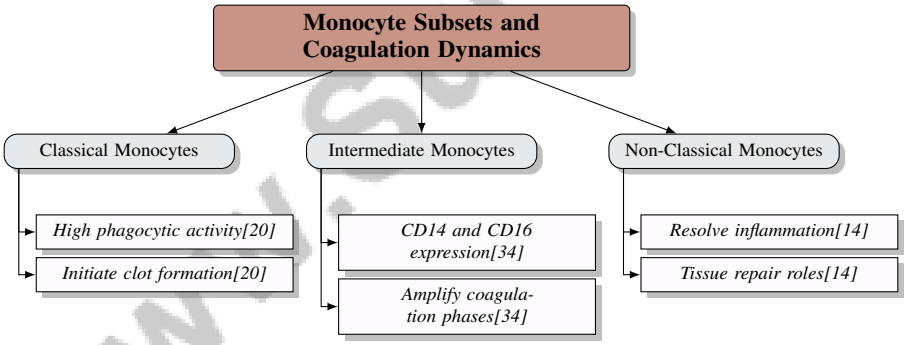

Figure 5: This figure illustrates the distinct roles of monocyte subsets in coagulation dynamics, highlighting classical, intermediate, and non-classical monocytes' contributions to coagulation processes, inflammation resolution, and tissue repair.

5.3 Technological Advances in Measuring Coagulation Influences

Technological advancements have significantly improved the measurement and understanding of monocyte influences on coagulation processes. Magnetic particle imaging (MPI) effectively detects changes in blood viscosity associated with coagulation, providing a non-invasive method to monitor coagulation dynamics and monocyte-coagulation pathway interactions [37].

Additionally, a generalized storage model has been proposed to better capture dynamics and cluster distributions in aerosol systems, analogous to coagulation processes involving monocytes, enhancing understanding of coagulation factor distribution and behavior [35].

Advanced methodologies now allow real-time monitoring of coagulation factor interactions on live cell membranes, offering a more accurate depiction of the kinetics involved in coagulation processes and enabling observation of surface-dependent interactions critical for initiating and propagating coagulation cascades [32].

Studies, particularly those examining COVID-19 patients, have highlighted significant differences in coagulation profiles across disease severity groups, underscoring the importance of precise measurement techniques in understanding the pathological mechanisms underlying coagulation dysfunction [38]. Integrating these technological advances into clinical practice can enhance diagnostic accuracy and inform therapeutic strategies, particularly regarding COVID-19-related coagulation dysfunction [31].

These innovations are essential for elucidating the intricate interactions between monocyte subsets and coagulation processes, pivotal in hemostasis and thrombus formation. Leveraging advancements in genetic sequencing and transcriptomic analysis will deepen understanding of functional distinctions among monocyte populations and their roles in thrombotic and cardiovascular diseases, ultimately aiding in developing targeted therapeutic interventions to mitigate these conditions [14, 33].

6 Link to Cardiovascular Diseases

Recent insights into cardiovascular diseases (CVD) have highlighted the complex interactions among biological systems, particularly the role of CD16+ monocytes in inflammation and immune responses that drive cardiovascular pathology. This section explores the mechanisms by which CD16+ monocytes influence cardiovascular health, emphasizing their contributions to inflammatory processes and disease progression.

6.1 Cardiovascular Diseases: Pathophysiological Mechanisms

CD16+ monocytes, especially the non-classical subset, are pivotal in CVD pathophysiology, engaging in endothelial surveillance and inflammation, central to atherosclerosis and other cardiovascular conditions. Their interactions with activated platelets facilitate monocyte recruitment and endothelial adhesion, promoting atherosclerotic lesion progression [18]. Soluble CD62P, indicative of platelet activation, correlates with disease activity in cardiovascular contexts, underscoring the link between immune activation and cardiovascular risk [18].

The dynamics of inflammatory and patrolling monocytes significantly impact outcomes in systemic inflammatory responses, such as Gram-negative sepsis, relevant to CVD due to systemic inflammation's role in endothelial dysfunction [16]. Identifying therapeutic targets involves modulating monocyte subset activity and their interactions with immune cells and platelets, potentially reducing inflammation and improving outcomes in heart failure and coronary atherosclerosis [20, 3, 17, 1].

6.2 Inflammation and Cardiovascular Disease

Inflammation is a critical driver of CVD, linking risk factors to atherosclerosis. CD16+ monocytes adhere to the endothelium, differentiating into macrophages that form foam cells, key in plaque development [18]. Monocyte interactions with immune cells and platelets exacerbate vascular inflammation, increasing risks of events like myocardial infarction. The dynamic nature of monocyte subsets, particularly intermediate and non-classical, is crucial in chronic inflammation and tissue repair [13].

Chronic inflammation in CVD is linked to metabolic dysfunction, where cytokines from monocytes contribute to insulin resistance and dyslipidemia, heightening cardiovascular risk [29]. Targeting inflammatory pathways and modulating monocyte activity, especially CD16+ monocytes associated with low HDL-C, may stabilize plaques and improve outcomes [3, 17]. This highlights anti-inflammatory therapies' potential in CVD management.

6.3 Immunometabolic Interface and Cardiovascular Risk

The immunometabolic interface, marked by metabolic and immune interactions, significantly impacts cardiovascular risk, especially in obesity and diabetes [29]. In obesity, CD16+ monocytes in adipose tissue produce cytokines that promote insulin resistance and atherosclerosis [29]. Diabetes exacerbates these risks through altered metabolism, enhancing oxidative stress and endothelial dysfunction, which are linked to monocyte-driven plaque formation [29].

The interface underscores metabolic health's role in immune homeostasis, where dysregulation triggers chronic inflammation and tissue damage, central to CVD pathophysiology. Inflammatory signaling pathways activated by metabolic disruptions lead to chronic inflammation, compromising tissue integrity and advancing CVD [29, 25, 3, 9].

Understanding the immunometabolic interface is crucial for developing strategies targeting metabolic and inflammatory pathways, reducing cardiovascular risk. Addressing this interface can mitigate metabolic disorders' adverse effects on cardiovascular health, leveraging the relationship between immune responses and metabolic processes to maintain tissue homeostasis and prevent complications [17, 4, 29, 8, 3]. This integrated approach offers innovative treatment avenues in cardiovascular medicine.

7 Current Research and Future Directions

Category	Feature	Method
Gaps in Current Research	Real-Time Monitoring Methodological Standardization	SPION-AMF[37] APICE[18], BDM[10]
Potential Areas for Future Investigation	Cellular Dynamics	FCA[21], FMGS[11]

Table 1: This table presents a summary of current research gaps and potential areas for future investigation in the study of CD16+ monocytes. It highlights specific methodologies such as SPION-AMF for real-time monitoring and APICE and BDM for methodological standardization, as well as potential research areas including cellular dynamics, employing FCA and FMGS methods.

The field of immunology has increasingly emphasized the roles of CD16+ monocytes in immune responses and disease mechanisms. Table 1 delineates the existing gaps in CD16+ monocyte research and identifies promising directions for future investigations, emphasizing the need for advanced methodologies and innovative research approaches. Additionally, Table 2 provides a detailed examination of the current advancements, gaps, and future directions in CD16+ monocyte research, emphasizing the need for innovative methodologies and applications in the field. This section explores recent advancements in characterizing these monocytes and their implications for health and disease.

7.1 Advancements in Understanding CD16+ Monocytes

Recent studies have significantly enhanced our understanding of CD16+ monocytes, particularly their heterogeneity and the impact of lifestyle factors on their functions, paving the way for targeted therapeutic strategies in chronic diseases [1]. A novel five-marker gating strategy has refined the classification of monocyte subsets, surpassing traditional methods and facilitating precise assessments of monocyte perturbations in various pathological conditions [11]. This innovation is crucial for risk stratification in clinical settings, as evidenced in heart failure management [17].

As illustrated in Figure 6, the hierarchical categorization of CD16+ monocytes highlights their subsets, advancements in classification methods, and clinical implications in disease management. Bayesian dependence modeling has illuminated gene dependencies, paralleling advancements in understanding CD16+ monocytes and their complex interactions within the monocyte interactome, aiding the identification of novel therapeutic targets [10]. These insights are vital for chronic inflammatory conditions like obesity, atherosclerosis, and neurodegenerative diseases, where monocyte subsets' phenotypic and functional characteristics are influenced by aging and immune challenges. Ongoing research into CD16+ monocytes is essential for discovering new therapeutic targets for conditions such as sepsis and age-related immune dysfunction [14, 13, 1, 16].

7.2 Gaps in Current Research

Despite progress, significant gaps in CD16+ monocyte research hinder a comprehensive understanding of their roles in disease and therapeutic applications. The lack of standardized methodologies leads to discrepancies in identifying and characterizing monocyte subsets, particularly the intermediate subset [14]. This variability complicates findings and impedes consensus within the field. Additionally, the mechanisms by which monocyte subsets contribute to chronic inflammatory diseases remain poorly understood, limiting effective therapeutic development [1].

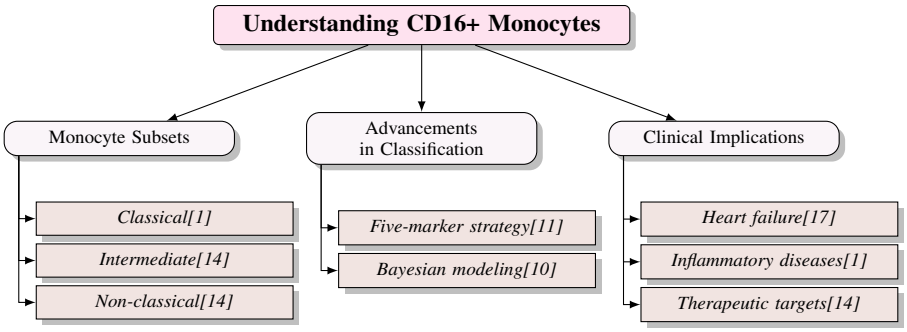

Figure 6: This figure illustrates the hierarchical categorization of CD16+ monocytes, highlighting their subsets, advancements in classification methods, and clinical implications in disease management.

The reliance on in vitro models that may not accurately reflect in vivo interactions in chronic inflammatory conditions further constrains our understanding [18]. There is an urgent need for sophisticated models replicating physiological environments to elucidate real-world implications of monocyte activity. Unanswered questions remain about the signals governing monocyte differentiation in humans and the long-term functional implications of these cells [7].

In coagulation research, existing methods often lack sensitivity and precision, especially for real-time monitoring of coagulation dynamics [37]. A comprehensive understanding of platelet-coagulation interplay is necessary for accurate diagnosis and treatment [33]. Furthermore, current methods for modeling conditional independence reflect gaps in understanding CD16+ monocyte functions, indicating a need for robust analytical approaches [10].

Additional gaps exist in understanding specific inflammatory pathways and their interactions with heart failure mechanisms, particularly in differentiating types of inflammation [4]. The immunopathogenesis of conditions like giant cell arteritis (GCA) and polymyalgia rheumatica (PMR) remains unclear, particularly regarding different monocyte subsets' roles [20]. In chronic lymphocytic leukemia (CLL), research gaps concerning monocyte subpopulation functional differences hinder a comprehensive understanding of their impact on the immune system [21].

The complexity of the senescence process and variability in monocyte responses among individuals challenge characterizing monocyte functions [12]. Long-term effects of coagulation dysfunction in COVID-19 survivors and optimal management strategies for diverse patient populations require further exploration [31]. Significant gaps remain in understanding how immune responses affect long-term neurological outcomes, particularly with comorbidities [8], and inflammation mechanisms across organ systems and their systemic interactions [9].

The retrospective nature and single-center designs of certain studies may limit the generalizability of findings, necessitating multi-center studies to validate results [38]. Selection bias in cohorts, such as predominantly male patients with ischemic heart disease, further restricts the applicability of research findings [17]. Addressing these gaps is crucial for advancing our understanding of CD16+ monocytes in health and disease.

7.3 Potential Areas for Future Investigation

Future research on CD16+ monocytes should prioritize several key areas to deepen understanding of their roles in health and disease. One critical area is exploring the functional implications of monocyte subpopulation dynamics in chronic lymphocytic leukemia (CLL) and their potential roles in therapeutic interventions [21]. Insights into these dynamics could inform targeted therapies aimed at modulating monocyte activity to enhance patient outcomes.

Investigating the prognostic value of serial monocyte measurements and other inflammatory markers across various disease contexts is another promising direction [17]. This could lead to improved risk stratification and personalized treatment strategies, particularly in inflammatory and cardiovascular diseases.

The mechanisms driving senescent monocyte accumulation in aging and their inflammatory effects warrant further investigation. Targeted therapies to mitigate these effects could significantly impact

age-related inflammatory diseases [12]. Additionally, longitudinal studies exploring the long-term implications of coagulation dysfunction in COVID-19 and developing standardized treatment protocols based on emerging evidence are essential research priorities [31].

Integrating clinical and preclinical findings to explore the gut-brain axis and systemic immunity in stroke recovery is another vital research avenue [8]. Such studies could illuminate the complex interactions between systemic inflammation and neurological outcomes.

Validation of the five-marker strategy for monocyte subset identification across different inflammatory conditions is necessary, alongside the exploration of additional markers to enhance subset identification [11]. This refinement could improve diagnostic and therapeutic approaches across various inflammatory diseases.

Finally, developing targeted therapies to modulate inflammatory responses and exploring novel biomarkers for inflammation-related diseases are crucial areas for future research [9]. These efforts will contribute to a comprehensive understanding of CD16+ monocytes, paving the way for innovative therapeutic strategies.

7.4 Technological and Methodological Innovations

Recent technological and methodological advancements have significantly enhanced the study of CD16+ monocytes, providing deeper insights into their roles in inflammation and immune responses. Advanced single-cell technologies have emerged as a promising innovation, enabling high-resolution analysis of monocyte behavior at the individual cell level and uncovering functional heterogeneity and novel therapeutic targets in chronic inflammatory conditions [1].

Single-cell RNA sequencing (scRNA-seq) has become a powerful tool for dissecting the transcriptomic landscape of monocyte subsets, allowing researchers to identify previously unrecognized functional states and pathways driving disease processes. This technology facilitates accurate identification of distinct monocyte subpopulations—classical, intermediate, and non-classical—by employing advanced genetic sequencing and multi-marker approaches. Understanding these subpopulations' unique surface marker expressions and functional properties is critical for elucidating their dynamic responses to inflammatory stimuli and their interactions with other immune cells, thereby enhancing our understanding of their roles in various chronic diseases, including atherosclerosis, obesity, and neurodegenerative disorders [11, 14, 1].

Advancements in flow cytometry and mass cytometry (CyTOF) have further improved the precision of monocyte phenotyping, enabling the distinction between the three major human monocyte subsets based on their unique surface marker expressions and functional properties. This progress allows for a deeper understanding of monocyte population heterogeneity and their roles in chronic inflammatory diseases, facilitating the identification of novel subpopulations and potential therapeutic targets [14, 1]. These methodologies enable simultaneous measurement of multiple surface markers and intracellular proteins, providing a comprehensive overview of monocyte activation states and functional capacities. The integration of these technologies with computational approaches, such as machine learning algorithms, enhances the classification of monocyte subsets and prediction of their roles in disease progression.

Innovations in imaging techniques, including high-resolution confocal microscopy and intravital imaging, have significantly improved our understanding of the dynamic interactions among monocyte subsets within various tissues. These advancements allow for real-time visualization and analysis of monocyte behavior, shedding light on their differentiation into macrophages or dendritic cells and their functional roles in both healthy and pathological conditions [14, 7]. Such insights are crucial for developing targeted therapies aimed at modulating monocyte activity in diseases.

The recent advancements in genetic sequencing, single-cell transcriptomics, and mass cytometry technologies are essential for enhancing our understanding of monocyte heterogeneity, functional distinctions, and their roles in various diseases. These innovations significantly propel the field of monocyte research forward, providing the necessary tools to elucidate the complex roles of CD16+ monocytes in health and disease and paving the way for targeted therapeutic strategies that improve clinical outcomes [11, 14, 1, 7].

Feature	Advancements in Understanding CD16+ Monocytes	Gaps in Current Research	Potential Areas for Future Investigation
Methodology	Five-marker Gating	IN Vitro Models	Serial Monocyte Measurements
Application	Risk Stratification	Chronic Inflammatory Diseases	Risk Stratification
Innovation	Bayesian Dependence Modeling	Not Specified	Novel Biomarkers

Table 2: This table presents a comprehensive overview of the advancements in understanding CD16+ monocytes, highlighting existing research gaps and potential areas for future investigation. It compares methodologies, applications, and innovations, thereby illustrating the current state and future directions in CD16+ monocyte research. The table underscores the importance of novel approaches for enhancing risk stratification and identifying new biomarkers.

8 Conclusion

The survey elucidates the pivotal involvement of CD16+ monocytes in thrombotic and cardiovascular diseases, with a focus on their roles in inflammation, immune response, and coagulation. The discovery of three distinct monocyte subsets—classical, intermediate, and non-classical—illustrates the functional diversity inherent within these cell populations, which is crucial for comprehending their varied contributions to both health and disease. This complexity highlights the necessity for targeted therapeutic approaches aimed at modulating specific monocyte functions to enhance clinical outcomes.

The interaction between CD16+ monocytes and coagulation pathways, especially in the context of inflammatory diseases such as COVID-19, accentuates the importance of thorough thrombotic risk assessment and the potential advantages of integrating anticoagulation with additional treatments. A deeper understanding of monocyte-coagulation dynamics is imperative for crafting effective strategies to reduce thrombotic risks and improve patient management.

Additionally, the inflammatory mediators produced by CD16+ monocytes are central to driving inflammatory responses, underscoring the need for developing potent anti-inflammatory therapies. Ongoing research into both synthetic and natural therapeutic agents is vital to overcoming the challenges posed by chronic inflammation.

Technological advancements, including microrheology, provide insights into the relationship between fibrin network architecture and mechanical properties, offering promising applications in the diagnosis of hypercoagulability. These innovations advance our comprehension of monocyte interactions with the coagulation system and aid in the creation of more precise diagnostic and therapeutic methods.

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