Macrophages and Cancer-Associated Cachexia: A Survey

Abstract

This survey paper delves into the intricate roles of macrophages within the tumor microenvironment, focusing on their contribution to cancer-associated cachexia and sarcopenia. Tumor-associated macrophages (TAMs) exhibit significant plasticity, transitioning between pro-inflammatory M1 and anti-inflammatory M2 phenotypes, thus influencing cancer progression and therapeutic outcomes. The paper underscores the dual role of TAMs in modulating immune responses and promoting muscle degradation through complex metabolic pathways. It highlights the metabolic adaptations of macrophages, emphasizing the impact of lipolysis, lipogenesis, and adipose tissue browning on cachexia. The survey further explores the pro-inflammatory and anti-inflammatory dynamics within the tumor microenvironment, detailing the balance maintained by macrophages and their regulatory mechanisms. Advanced imaging techniques and spatial analysis are discussed as critical tools for assessing muscle wasting and understanding the spatial dynamics of immune cells. The paper concludes by identifying potential therapeutic targets and biomarkers, advocating for comprehensive strategies that integrate nutritional, exercise, and pharmacological interventions to mitigate the effects of cachexia. Future research directions emphasize the need for refined diagnostic criteria, novel therapeutic approaches, and robust computational models to enhance our understanding and management of cancer-associated cachexia and sarcopenia.

1 Introduction

1.1 Interconnected Biological Concepts

The interplay among macrophages, cancer-associated cachexia, and sarcopenia forms a complex network that significantly impacts cancer progression. Tumor-associated macrophages (TAMs) are pivotal in this network, displaying dual roles in tumor growth promotion and immune suppression [1]. Their capacity to polarize into pro-inflammatory M1 and anti-inflammatory M2 phenotypes allows them to adapt to environmental stimuli, thereby modulating the tumor microenvironment [2]. This plasticity is essential for cancer invasion and progression, as TAMs can either exacerbate or mitigate inflammation, influencing therapeutic responses and disease outcomes [3].

Cancer-associated cachexia is a multifactorial syndrome characterized by severe weight loss, muscle wasting, and systemic inflammation, affecting 50–80% of cancer patients and contributing to 20% of cancer-related deaths. The involuntary loss of skeletal muscle and adipose tissue is particularly pronounced in patients undergoing treatment. Sarcopenia, marked by progressive skeletal muscle mass and strength loss, is closely related to cachexia, as both conditions involve muscle degradation. The inflammatory environment within the tumor, driven by macrophage activity, exacerbates muscle wasting through catabolic processes and disruption of metabolic regulation [3].

Furthermore, macrophage metabolic adaptations in response to cancer are crucial for their functional roles within the tumor microenvironment [4]. Understanding the context-specific roles of macrophages is vital, as they are central to both promoting and resolving inflammation, thereby

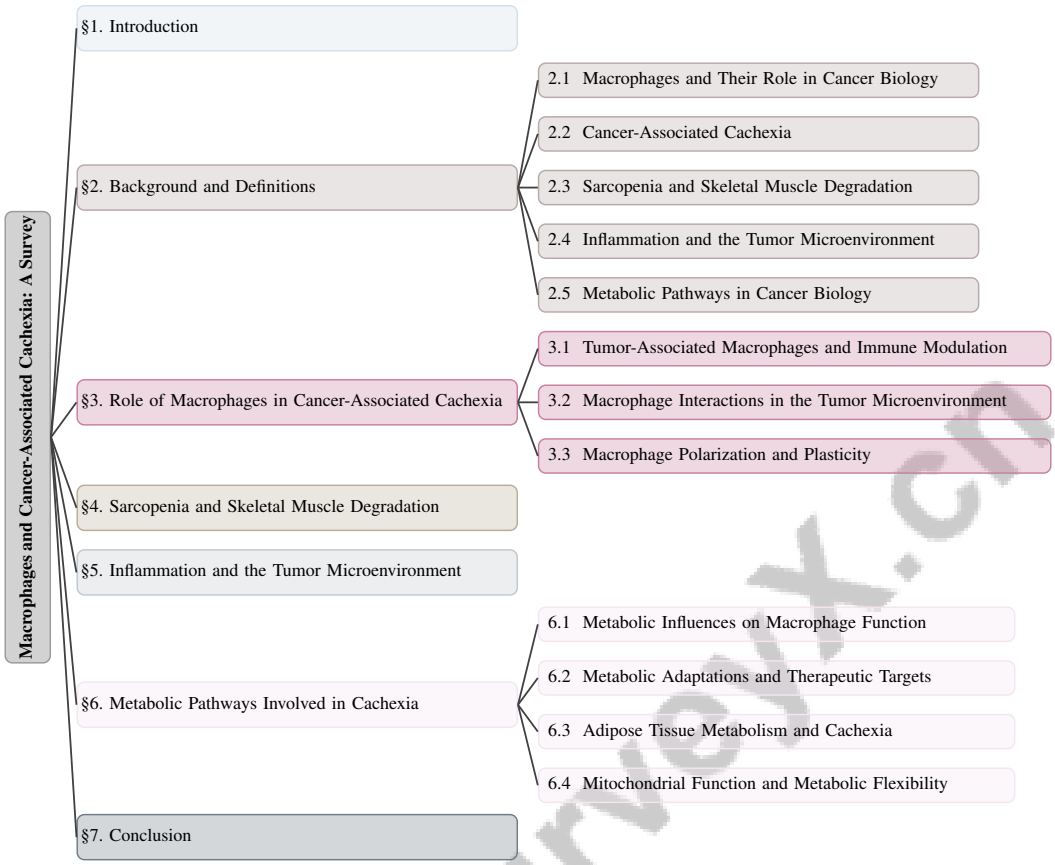

Figure 1: chapter structure

influencing cancer-associated cachexia and sarcopenia. This interconnectedness underscores the potential of targeting macrophage activity and metabolic pathways as therapeutic strategies in cancer treatment [5].

1.2 Significance in Cancer Progression

The interconnected roles of macrophages, cancer-associated cachexia, sarcopenia, and the tumor microenvironment are critical for understanding cancer progression. TAMs exhibit both pro-tumorigenic and anti-tumorigenic properties based on their M1 or M2 polarization [1]. This duality is significant as it affects the tumor microenvironment (TME), where the balance between these phenotypes can either promote or inhibit tumor growth. The TME is a dynamic entity, with interactions among cancer cells and various components, including macrophages, driving metastasis and tumor dissemination [6].

Cancer-associated cachexia, characterized by severe muscle and fat loss unresponsive to nutritional support, adversely affects cancer progression by diminishing quality of life and survival rates. The persistent loss of skeletal muscle mass in cachexia correlates with poor prognosis and reduced treatment efficacy. The inflammatory milieu, intensified by TAMs, disrupts normal metabolic processes and complicates cancer management, emphasizing the need to understand these interactions for effective therapeutic strategies [7].

Moreover, the absence of comprehensive models to elucidate macrophage dynamics during inflammation hampers the development of effective therapeutic interventions [8]. The diversity of macrophages and their roles in tissue homeostasis are integral to cancer progression [9]. These insights are essential for advancing therapeutic strategies aimed at modulating the tumor microenvironment and alleviating the systemic effects of cancer-associated cachexia and sarcopenia. Understanding the complex interplay between macrophage activity, metabolic pathways, and immune interactions is crucial for improving cancer treatment outcomes.

1.3 Structure of the Survey

This survey is structured to provide a comprehensive exploration of macrophages' roles in cancer-associated cachexia and sarcopenia, mapping the complex interactions within the tumor microenvironment and metabolic pathways. The **Introduction** sets the foundation by elucidating the interconnected biological concepts and their significance in cancer progression. Following this, the **Background and Definitions** section defines key terms such as macrophages, cancer-associated cachexia, sarcopenia, skeletal muscle degradation, inflammation, tumor microenvironment, and metabolic pathways within cancer biology.

The section **Role of Macrophages in Cancer-Associated Cachexia** examines how macrophages contribute to cachexia, focusing on their roles in skeletal muscle degradation and inflammation. It highlights macrophages' dual role in promoting and resolving inflammation, with subsections dedicated to tumor-associated macrophages, immune modulation, and macrophage polarization. The subsequent section, **Sarcopenia and Skeletal Muscle Degradation**, investigates the mechanisms of sarcopenia and the impact of macrophage activity on muscle wasting in cancer patients.

The section on **Inflammation and the Tumor Microenvironment** analyzes inflammation's role, emphasizing the dynamics between pro-inflammatory and anti-inflammatory signals and their implications for cancer progression and cachexia. The survey further explores **Metabolic Pathways Involved in Cachexia**, discussing complex metabolic interactions and potential therapeutic targets, including the influence of metabolic changes on macrophage function, adipose tissue metabolism, and mitochondrial function.

Finally, the **Conclusion** synthesizes key insights and proposes future research directions and therapeutic strategies, addressing therapeutic implications, potential biomarkers, and the use of spatial analysis and imaging techniques in studying cachexia. This structured approach ensures a thorough understanding of the multifaceted roles of macrophages in cancer-associated cachexia and sarcopenia.The following sections are organized as shown in Figure 1.

2 Background and Definitions

2.1 Macrophages and Their Role in Cancer Biology

Macrophages are pivotal immune cells integral to tissue homeostasis and immune regulation, exhibiting functional diversity influenced by their origins and microenvironmental signals. Within tumors, they differentiate into tumor-associated macrophages (TAMs), which are polarized into M1 and M2 phenotypes. M1 macrophages produce pro-inflammatory cytokines with anti-tumor effects, whereas M2 macrophages promote tumor growth through immunosuppression and angiogenesis [10, 11, 12]. The microenvironment's mechanical properties further modulate macrophage activation and function [13].

Macrophages utilize complex signaling networks to respond to foreign challenges, and computational models offer insights into their behavior within the tumor microenvironment [14, 8]. Understanding these dynamics is essential for devising therapeutic strategies to modulate the tumor microenvironment and enhance cancer treatment outcomes [5].

2.2 Cancer-Associated Cachexia

Cancer-associated cachexia (CAC) is a syndrome characterized by involuntary weight loss and muscle wasting, critically affecting prognosis and survival, especially in non-small cell lung cancer (NSCLC) [15]. CAC involves metabolic abnormalities driven by tumor-host interactions, leading to significant body mass depletion and diminished quality of life, exacerbated by tumor-induced immune disorders [3]. Browning of white adipose tissue (WAT) precedes weight loss, indicating a metabolic shift contributing to CAC's catabolic state [2].

Muscle mass loss in CAC correlates with poor prognosis and reduced treatment efficacy [16]. Understanding CAC's mechanisms is crucial for developing targeted interventions to improve patient quality of life and treatment efficacy.

2.3 Sarcopenia and Skeletal Muscle Degradation

Sarcopenia, an age-related syndrome, involves progressive loss of skeletal muscle mass, strength, and function, increasing disability risks [17]. In cancer patients, sarcopenia exacerbates cachexia, driven by tumor-induced metabolic and inflammatory changes that accelerate muscle wasting [18, 19]. This muscle loss limits patients' ability to endure aggressive treatments, often requiring dose adjustments [15].

Accurate sarcopenia assessment is vital for optimizing cancer treatment, with CT scans at the L3 vertebral level commonly used to evaluate muscle mass [20]. Traditional methods are labor-intensive, necessitating advanced imaging solutions [21]. Addressing sarcopenia requires resistance exercise and adequate protein intake [22]. Understanding neurogenic components is crucial, as current treatments often overlook these factors [23]. Elucidating sarcopenia mechanisms enables effective management strategies to enhance muscle preservation and treatment efficacy.

2.4 Inflammation and the Tumor Microenvironment

Inflammation is a complex response involving immune cell recruitment, which, while protective, can be detrimental in cancer by contributing to metabolic dysregulation and disease progression [24]. The tumor microenvironment (TME), comprising cancer cells, immune cells, cancer-associated fibroblasts (CAFs), and an extracellular matrix (ECM), significantly influences cancer progression and therapeutic resistance [25, 26].

Macrophages in the TME exhibit plasticity, responding to signals that modulate their phenotypes and functions [27]. The balance between pro-inflammatory and anti-inflammatory signals is crucial for cancer trajectory determination [9, 28]. Understanding macrophage activation pathways is vital for therapeutic development [12].

The TME's mechanical properties influence cell fate and behavior [13]. Computational models, incorporating multiplex immunohistochemistry data, enhance understanding of immune responses and macrophage dynamics in cancer progression [29, 8].

Inflammation from cancer-associated processes modulates TME immune responses, crucial for cancer progression [5]. Mitochondria influence inflammatory pathways, with mitochondrial DAMP signaling integral to these responses [30]. Understanding inflammation-TME interactions enhances immune modulation and therapeutic efficacy, improving patient outcomes and overcoming resistance [31, 4].

2.5 Metabolic Pathways in Cancer Biology

Metabolic pathways are vital for understanding tumor-microenvironment interactions, supporting rapid cancer cell proliferation, and influencing systemic metabolic alterations in cachexia and sarcopenia. These pathways regulate muscle stem cell (MuSC) behavior, impacting muscle regeneration and maintenance in cancer patients [32].

Macrophage metabolism, influenced by local microenvironments, displays flexibility, adapting to the tumor microenvironment to either support or inhibit tumor growth [33]. Adipose tissue metabolism is pivotal in cancer-associated cachexia, affecting energy balance and muscle mass loss. White adipose tissue browning, mediated by Glucose-regulated protein 75 (GRP75), contributes to the cachectic state [2].

Systemic inflammation and tumor metabolism impact cachexia's biochemical characteristics, with tumor demands exacerbating energy deficits and muscle wasting [19]. GDF15, inducing weight loss via the GFRAL-RET pathway, emerges as a therapeutic target, offering intervention opportunities in cancer cachexia [34].

These metabolic pathways interact with cellular mechanisms, including oxidative stress, implicated in sarcopenia pathophysiology. Prevention and treatment strategies for sarcopenia focus on mitigating oxidative stress through exercise and nutrition, emphasizing metabolic homeostasis in cancer patients [35]. Understanding these networks is crucial for developing therapies targeting cancer cells' metabolic vulnerabilities and host interactions, improving patient outcomes and quality of life.

3 Role of Macrophages in Cancer-Associated Cachexia

Macrophages are critical players in cancer-associated cachexia, extending their roles beyond traditional immune functions to include immune modulation and metabolic regulation. This section explores the impact of tumor-associated macrophages (TAMs) on the tumor microenvironment and cachexia, highlighting their interactions with other immune cells. Understanding these dynamics is crucial for comprehending their dual roles in tumor progression and cachexia-related effects.

To further elucidate these concepts, Figure 2 illustrates the hierarchical structure of the role of macrophages in cancer-associated cachexia. This figure highlights their immune modulation, interactions within the tumor microenvironment, and the processes of polarization and plasticity. It categorizes macrophages into distinct types and functions, explores therapeutic strategies, and examines advanced analysis techniques and challenges in understanding macrophage dynamics. By integrating this visual representation, we can better appreciate the complexity of macrophage involvement in the pathophysiology of cachexia.

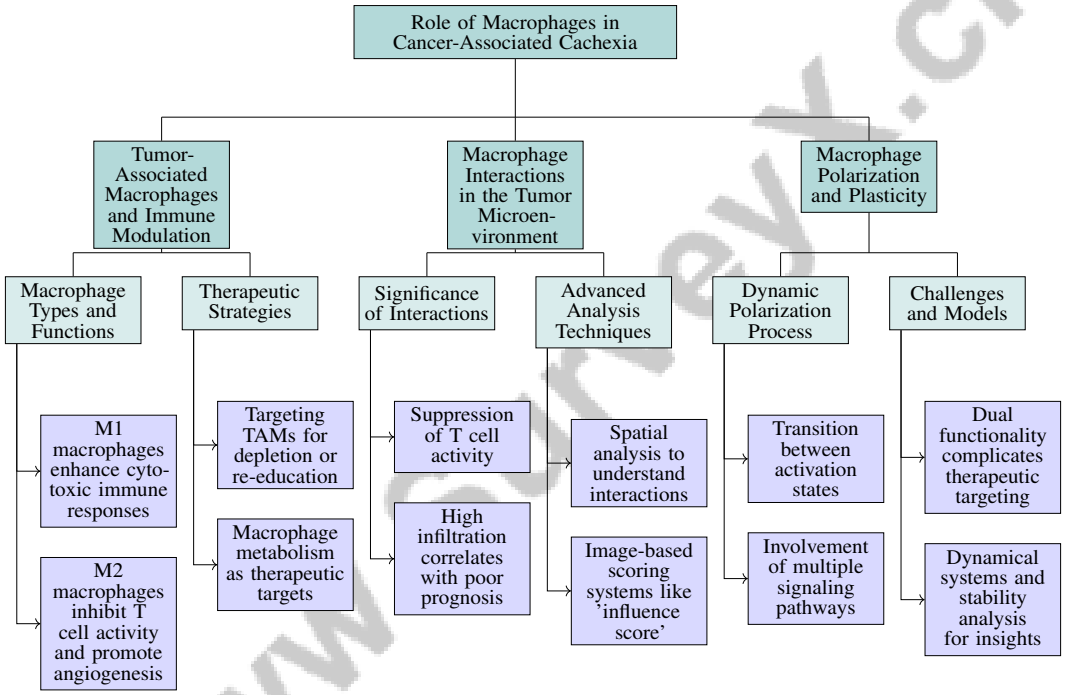

Figure 2: This figure illustrates the hierarchical structure of the role of macrophages in cancer-associated cachexia, highlighting their immune modulation, interactions within the tumor microenvironment, and polarization and plasticity. It categorizes macrophages into distinct types and functions, explores therapeutic strategies, and examines advanced analysis techniques and challenges in understanding macrophage dynamics.

3.1 Tumor-Associated Macrophages and Immune Modulation

TAMs are vital components of the tumor microenvironment, functioning in immune modulation with a dual role. They are categorized into M1 macrophages, which enhance cytotoxic immune responses, and M2 macrophages, which facilitate tumor progression by inhibiting T cell activity and promoting angiogenesis. Their plasticity enables transitions between these states in response to tumor microenvironment cues, significantly affecting cancer-associated cachexia and patient outcomes. Targeting TAMs is a promising therapeutic strategy, focusing on their depletion or re-education to enhance anti-tumor immunity [1, 36, 37, 38]. The ontogeny and functional state of TAMs are pivotal in determining their roles within the tumor milieu. A comprehensive framework categorizes macrophages based on their developmental origins and functions, providing insights into their diverse roles in tumor biology [39]. Macrophage metabolism plays a crucial role in adapting to metabolic challenges, underscoring their potential as therapeutic targets [10]. Systems biology approaches

integrating gene expression data with clinical parameters reveal complex interactions governing TAM behavior [14], which could inform strategies to reprogram TAMs from a pro-tumor M2 to an anti-tumor M1 phenotype [40].

The interactions between TAMs and other tumor microenvironment components underscore the complexity of immune modulation in cancer-associated cachexia. As illustrated in Figure 3, the figure highlights the key aspects of tumor-associated macrophages (TAMs), including their classification into M1 and M2 types, therapeutic strategies targeting TAMs, and their interactions within the tumor microenvironment (TME). Studies highlight the varying roles of TME components in metastasis, with some emphasizing the pro-tumorigenic roles of macrophages [6]. For instance, CAP treatment enhances TAM function, modulating immune responses in cancer contexts [5]. Targeting signaling pathways that regulate macrophage polarization may mitigate cancer-associated cachexia effects, thereby improving patient outcomes.

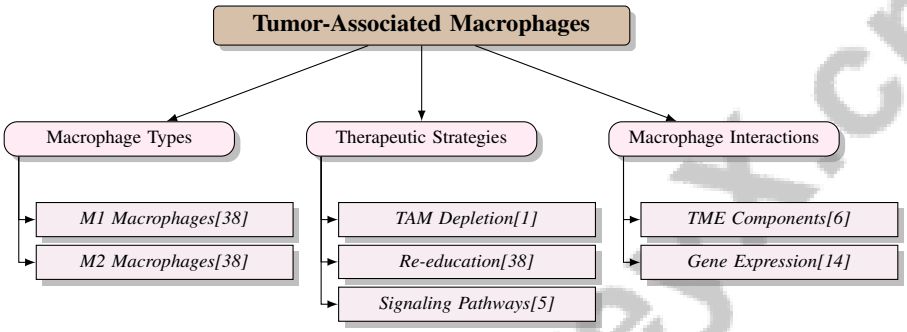

Figure 3: This figure illustrates the key aspects of tumor-associated macrophages (TAMs), including their classification into M1 and M2 types, therapeutic strategies targeting TAMs, and their interactions within the tumor microenvironment (TME).

3.2 Macrophage Interactions in the Tumor Microenvironment

Macrophage interactions with other cellular components in the tumor microenvironment (TME) are pivotal in shaping cancer progression and therapeutic responses. TAMs can either suppress T cell activity and promote tumor progression or, less frequently, enhance anti-tumor responses depending on their activation state. Their high infiltration in tumor tissues correlates with poor patient prognosis, making TAMs a focal point for therapies aimed at depleting or re-educating them to support immune responses against tumors [36, 38]. These interactions are governed by complex signaling networks and spatial relationships that influence tumor behavior and treatment responses.

Recent advancements in spatial analysis techniques have enhanced our understanding of these interactions. The categorization of research into first-order and second-order analyses has proven instrumental in examining spatial relationships between cell types within the TME [26]. This nuanced understanding of macrophage and immune cell distribution impacts tumor progression.

Moreover, novel image-based scoring systems, such as the 'influence score', quantify the impact of tumor regions on immune cells through spatial analysis [29]. This method enhances our ability to characterize complex TME interactions and assess macrophage influence on tumor dynamics. Mechanistic models have also evolved to incorporate the mechanical aspects of tumor growth, transitioning from ordinary differential equation (ODE) to partial differential equation (PDE) models, thus offering a comprehensive understanding of the TME [4]. These models highlight mechanical forces' role in modulating macrophage interactions and their effects on tumor behavior.

Therapeutic strategies targeting macrophage activity within the TME focus on inhibiting cytokines and chemokines that recruit pro-tumor macrophages while activating their anti-tumor functions [41]. Such strategies aim to shift the balance towards an anti-tumorigenic environment, enhancing cancer therapy efficacy.

Despite advancements, challenges remain in fully understanding TME interactions. Traditional methods, such as persistent homology, face limitations in analyzing multispecies data, crucial for capturing biological interaction complexity [42]. Addressing these limitations is vital for developing

accurate models that predict and manipulate macrophage interactions within the TME, ultimately improving cancer treatment outcomes.

3.3 Macrophage Polarization and Plasticity

Macrophage polarization within the TME is a dynamic process significantly influencing cancer progression and cachexia. This process is characterized by macrophages' ability to transition between various activation states, beyond the traditional M1 (pro-inflammatory) and M2 (anti-inflammatory) phenotypes. The regulatory mechanisms governing macrophage polarization are intricate, involving multiple signaling pathways that define their functional roles in the TME [43].

Macrophage plasticity presents a substantial challenge for therapeutic targeting, enabling them to perform both pro-tumorigenic and anti-tumorigenic functions [41]. This dual functionality complicates the development of strategies aimed at modulating macrophage activity for beneficial therapeutic outcomes. Theoretical models employing dynamical systems and stability analysis of ordinary differential equations provide insights into the stability and transitions between different macrophage states, offering potential therapeutic avenues [44].

Additionally, macrophage heterogeneity across different tissue environments complicates understanding their physiological roles [45]. This complexity is reflected in their diverse functions, including tissue remodeling and immune responses, such as phagocytosing cells presenting phosphatidylserine (PtdSer), highlighting their extensive functional repertoire [46]. Computational approaches identify specific network motifs governing macrophage responses to varying stimuli, revealing distinct mechanisms for endotoxin tolerance and priming [14].

Understanding macrophage polarization and plasticity is crucial for elucidating their impact on cancer progression and cachexia. By analyzing the intricate signaling pathways and network topologies involved in macrophage activation, researchers can optimize strategies targeting TAMs. These strategies aim to modulate the TME, enhancing anti-tumor immune responses while mitigating TAMs' immunosuppressive effects, ultimately improving cancer treatment outcomes by addressing TAMs' dual roles in tumor progression and therapeutic resistance [36, 37, 41].

4 Sarcopenia and Skeletal Muscle Degradation

4.1 Mechanisms of Sarcopenia

Sarcopenia, characterized by a decline in skeletal muscle mass and function, presents significant challenges, particularly in cancer patients. Its pathophysiology involves complex mechanisms, including protein synthesis and degradation, mitochondrial dysfunction, and inflammatory responses influenced by the tumor microenvironment [47]. This environment disrupts metabolic and inflammatory pathways, exacerbating muscle degradation. Aging-related changes in nervous systems further contribute to muscle performance decline, emphasizing sarcopenia's multifactorial nature [23]. The continuum model for skeletal muscle tissue offers insights into these biological mechanisms, highlighting the loss of activation due to aging [48].

Macrophages, essential for tissue homeostasis, exhibit functional heterogeneity impacting sarcopenia progression [39]. Their roles in tissue repair and remodeling are crucial, particularly as immune cell infiltration into adipose tissue disrupts metabolic responses, exacerbating muscle wasting [1]. The interconnectedness of muscle, bone, and fat tissues introduces 'osteosarcopenia,' complicating sarcopenia's understanding [49]. Recognizing sarcopenia as a significant condition in older adults is crucial, given its links to frailty and adverse health outcomes [17].

Despite advances in understanding sarcopenia's mechanisms, consensus on optimal exercise types, intensity, and frequency remains elusive [35]. Future research should develop guidelines for diagnosing sarcopenia and explore lifestyle interventions, such as exercise and nutrition, to enhance muscle preservation and cancer treatment efficacy. Targeted interventions addressing these mechanisms can improve the quality of life and treatment outcomes for cancer patients affected by sarcopenia.

4.2 Role of Macrophages in Muscle Wasting

Macrophages play a central role in skeletal muscle degradation, particularly in cancer-associated cachexia and sarcopenia. Their impact on muscle wasting is closely linked to their polarization states, influencing inflammatory responses and muscle tissue outcomes [43]. In the tumor microenvironment, tumor-associated macrophages (TAMs) often adopt a pro-tumorigenic M2 phenotype, secreting anti-inflammatory cytokines that foster a catabolic environment conducive to muscle degradation [14]. This environment is further shaped by the biophysical properties of the microenvironment, modulating macrophage inflammatory gene expression and exacerbating muscle wasting [13].

Macrophages maintain tissue homeostasis and respond to microenvironmental cues, underscoring their physiological importance [48]. The continuum model elucidates how decreased activation, influenced by macrophage activity, contributes to muscle wasting, reinforcing the need to understand these interactions in sarcopenia [48]. Additionally, macrophages regulate metabolic pathways affecting muscle protein synthesis and degradation, linking them to sarcopenia's pathophysiology [23].

Addressing muscle wasting requires a multifaceted approach, integrating nutritional and physical exercise interventions to counteract sarcopenia and cachexia effects [17]. Identifying modifiable risk factors, such as physical inactivity and poor nutrition, highlights the potential for targeted interventions to enhance muscle mass and function, improving patient outcomes [47]. Advances in imaging techniques, such as CT scans, enable precise assessment of muscle mass loss, providing critical insights for therapeutic strategy development [49].

A comprehensive understanding of the interplay between macrophage activity, inflammatory responses, and metabolic pathways is essential for developing effective interventions against muscle wasting in cancer patients. Targeting the biochemical and metabolic mechanisms associated with cancer-induced cachexia and sarcopenia, such as inflammation-driven cytokine imbalances and energy expenditure dysregulation, can enhance treatment efficacy and significantly improve the quality of life for affected individuals. This approach may involve utilizing natural products and immunomodulatory strategies to combat muscle and fat loss, addressing both cachexia and age-related muscle mass decline [3, 18, 19, 47, 7].

5 Inflammation and the Tumor Microenvironment

5.1 Pro-inflammatory and Anti-inflammatory Dynamics

The tumor microenvironment (TME) is characterized by a dynamic balance between pro-inflammatory and anti-inflammatory signals, crucially influencing cancer progression and therapeutic outcomes. Central to this process are macrophages, which display significant plasticity, shifting between the pro-inflammatory M1 phenotype and the anti-inflammatory M2 phenotype in response to environmental cues. M1 macrophages are primarily involved in pathogen elimination and inflammation, whereas M2 macrophages promote tissue repair and suppress inflammatory responses [50]. The regulatory mechanisms governing macrophage polarization are complex, involving multiple signaling pathways that are not yet fully understood [45].

Understanding these pathways is essential for developing therapeutic strategies aimed at modulating macrophage activity to prevent excessive inflammation and enhance tissue repair [12]. Mitochondrial dysfunction and cellular stress responses further complicate this balance by activating pathways that influence macrophage behavior [30]. Soluble mediators within the TME play a pivotal role in maintaining the equilibrium of inflammatory signals, thus impacting macrophage phenotype balance [51]. The regulation of macrophage activity and their interactions with other TME components is also influenced by pro- and anti-phagocytic signals, including 'don't eat-me' signals like CD47 [46].

Moreover, macrophages' historical exposure to endotoxins can lead to tolerance or priming, affecting their responses [14]. A deeper understanding of macrophage dynamics is crucial for leveraging their therapeutic potential to modulate the TME and improve cancer treatment outcomes.

5.2 Inflammation and Tissue Repair

Inflammation within the tumor microenvironment (TME) plays a dual role, serving as both a protective mechanism and a contributor to chronic disease. Macrophages are key mediators of this inflammation,

transitioning between pro-inflammatory (M1) and anti-inflammatory (M2) states in response to various signals. M1 macrophages are associated with anti-tumor activities, promoting cytotoxic responses and phagocytosis of cancer cells, while M2 macrophages facilitate tumor progression through immune suppression, angiogenesis, and metastasis [12, 31, 41].

M1 macrophages respond to acute inflammation by producing cytokines and chemokines that recruit additional immune cells, essential for pathogen clearance and initiating tissue repair. Dysregulation of this response can lead to chronic inflammation and tissue damage, contributing to tumor progression and metastasis [12]. Conversely, M2 macrophages resolve inflammation and promote tissue repair through the secretion of anti-inflammatory cytokines and growth factors [50].

The balance between these macrophage phenotypes is crucial for determining inflammation outcomes in the TME, influenced by factors such as the local cytokine environment, cellular interactions, and metabolic cues [45]. 'Don't eat-me' signals like CD47 modulate macrophage activity, preventing excessive tissue damage while facilitating efficient repair mechanisms [46]. Additionally, the mechanical properties of the TME, including stiffness and composition, significantly impact macrophage behavior and their role in tissue repair [13].

Understanding macrophage polarization and function is vital for developing therapeutic strategies that harness their reparative potential while minimizing tissue damage. Targeting specific signaling pathways and modulating the inflammatory response could enhance tissue repair and improve outcomes in cancer patients. The complex interplay between inflammation and tissue repair within the TME underscores the dual role of tumor-associated macrophages (TAMs), which can either promote tumor growth and immunosuppression or facilitate cancer cell elimination and immune activation. This duality highlights the need for targeted therapeutic strategies to modulate macrophage activity, enhancing their antitumor functions while mitigating tumor-promoting effects, potentially improving treatment outcomes by addressing the dynamic interactions between immune and cancer cells in the TME [28, 1, 41].

6 Metabolic Pathways Involved in Cachexia

6.1 Metabolic Influences on Macrophage Function

The tumor microenvironment (TME) significantly influences macrophage behavior, particularly in cancer-associated cachexia. Tumor-associated macrophages (TAMs) exhibit adaptability, responding to metabolic cues within the TME, which is crucial for modulating immune responses and cancer progression [43]. Understanding the functional diversity of $Ly6C^{hi}$ and $Ly6C^{lo}$ macrophages is essential for developing strategies targeting metabolic pathways altered in cachexia [9].

Key metabolic pathways affecting macrophage function include lipolysis, lipogenesis, and adipose tissue browning [28]. Lipolysis provides energy substrates for macrophage activity, while lipogenesis supports biosynthetic demands. Adipose tissue browning, involving the conversion of white to brown adipose tissue, enhances energy expenditure and influences the TME's inflammatory milieu.

Integrating targeted and proteomic approaches reveals mechanisms of metabolic regulation and macrophage function [52]. Mathematical models further elucidate T cell and macrophage interaction dynamics, enhancing our understanding of metabolic influences in cachexia [40]. Exploring endotoxin tolerance and priming mechanisms in macrophages is crucial for understanding metabolic impacts on their function in cancer-associated cachexia [14]. Future research should clarify mitochondrial dysfunction's links to inflammation, aiming to develop targeted therapies for these pathways [30]. By elucidating metabolic influences on macrophage function, researchers can better harness their therapeutic potential to improve cancer treatment outcomes and mitigate cachexia effects.

6.2 Metabolic Adaptations and Therapeutic Targets

Investigating metabolic adaptations in cancer-associated cachexia (CAC) reveals critical therapeutic targets. Abnormal lipid metabolism is central, necessitating a multimodal approach combining nutritional support, exercise, and targeted therapies to address metabolic derangements [53]. Targeting pathways affecting muscle stem cells (MuSCs) highlights the potential of metabolic regulation to enhance muscle regeneration and alleviate muscle disorders [32].

Therapeutic interventions focusing on TME components emphasize understanding complex interactions for effective modulation [25]. Developing therapies targeting specific TME components while preserving immune function is vital for optimizing treatment efficacy and minimizing adverse effects [24]. Refining mathematical models to include additional cell types offers promising avenues for exploring therapeutic implications in complex biological systems [44].

Targeted therapies like KY-NAb-GDF15 represent advancements by specifically targeting GDF15, reducing off-target effects, and enhancing cachexia management efficacy [34]. Precision in targeting metabolic pathways promises improved patient outcomes and quality of life. Concurrently, optimizing methods to reduce contamination and enhance detection limits for secreted proteins could refine our understanding of metabolic processes in CAC [54]. Future research should prioritize identifying novel therapeutic targets within cachexia's metabolic pathways and developing early diagnostic tools for timely intervention [19]. Advancing our understanding of metabolic adaptations in CAC and refining therapeutic strategies can lead to more effective interventions addressing the complex interplay of contributing factors.

6.3 Adipose Tissue Metabolism and Cachexia

Adipose tissue metabolic abnormalities significantly contribute to cancer-associated cachexia (CAC), with both white adipose tissue (WAT) and brown adipose tissue (BAT) playing roles in the syndrome's pathophysiology [53]. In CAC, WAT undergoes remodeling characterized by increased lipolysis, releasing free fatty acids and glycerol, fueling tumor growth and exacerbating muscle wasting. This catabolic state is intensified by WAT browning, where white adipocytes adopt brown-like characteristics, enhancing mitochondrial activity and thermogenesis, increasing energy expenditure and weight loss [53].

BAT, known for its thermogenic role, becomes hyperactive in CAC, exacerbating the syndrome's energy imbalance. Activation of BAT and WAT browning is mediated by cytokines and signaling molecules from tumors and immune cells within the TME, including pro-inflammatory cytokines like TNF- and IL-6, which promote lipolysis in adipose tissues and influence systemic inflammation and metabolic dysregulation in cachexia [53].

The metabolic reprogramming of adipose tissue in CAC highlights potential therapeutic targets aimed at mitigating cachexia's impact. Strategies to inhibit lipolysis or block WAT browning may help preserve adipose tissue mass and reduce the catabolic burden on skeletal muscle. Additionally, targeting signaling pathways driving BAT activation and WAT browning could offer new therapeutic avenues, potentially improving energy balance and patient outcomes in CAC [53]. Understanding the interplay between adipose tissue metabolism and systemic energy homeostasis is essential for developing effective treatments for cancer-associated cachexia.

6.4 Mitochondrial Function and Metabolic Flexibility

Mitochondrial function and metabolic flexibility are critical in cancer-associated cachexia, influencing energy homeostasis and the syndrome's metabolic adaptations. Mitochondria, central organelles for energy production, maintain cellular metabolic flexibility, allowing adaptation to varying energetic demands and nutrient availability [53]. In cachexia, mitochondrial dysfunction impairs energy production and increases oxidative stress, exacerbating muscle wasting and systemic energy deficits.

Mitochondrial metabolic flexibility is vital for adapting to the catabolic state induced by cachexia, characterized by heightened energy substrate demands due to increased metabolic activity within the TME. This flexibility is compromised in cachexia, evidenced by altered mitochondrial dynamics and bioenergetics, restricting tissues' ability to efficiently switch between fuel sources, such as carbohydrates and fats. The resulting metabolic inflexibility contributes to cachexia progression by impairing muscle regeneration and promoting degradation [53].

Future research should expand datasets to include diverse populations and explore mechanistic pathways underlying gene expression changes related to mitochondrial function and metabolic flexibility [55]. Developing targeted therapies to enhance mitochondrial function and restore metabolic flexibility holds promise for mitigating cachexia effects. Such interventions could improve energy homeostasis, reduce oxidative stress, and support muscle preservation, ultimately enhancing patient outcomes in cancer-associated cachexia. Understanding the intricate relationship between mitochon-

drial function and metabolic flexibility is essential for devising effective therapeutic strategies against this debilitating condition.

7 Conclusion

7.1 Therapeutic Implications and Future Directions

Advancements in understanding the multifaceted roles of macrophages in cancer-associated cachexia (CAC) have opened novel therapeutic possibilities. Targeting immune dysregulation and inflammatory pathways offers potential enhancements in patient outcomes when combined with existing cancer treatments. Future investigations should prioritize elucidating the specific signals that regulate macrophage functions across different tissues. This includes exploring strategies to modulate tumor-associated macrophage (TAM) activities within diverse tumor microenvironments and cancer stages.

Combination therapies addressing various elements of the tumor microenvironment (TME) are crucial for enhancing treatment efficacy and minimizing metastasis. Delving into the signaling pathways that govern macrophage polarization is vital for restoring inflammatory equilibrium and improving therapeutic results. Additionally, understanding the muscle stem cell (MuSC) niche interactions and utilizing metabolic regulation for muscle regeneration present promising therapeutic avenues. Enhancing apoptotic cell clearance may also modulate immune responses within CAC.

Comprehending the contextual protein interaction networks is essential for understanding macrophage behavior during infections. Experimental validation of model predictions and examination of additional TME components can inform potential cachexia treatments. Enhancing computational models for efficiency and empirical validation remains a priority.

Recognizing sarcopenia as a significant healthcare challenge emphasizes the role of imaging in diagnosis and monitoring. Research should aim to establish standardized diagnostic criteria, explore effective interventions, and assess the roles of nutrition and exercise in sarcopenia prevention. Validating circulating microRNAs as biomarkers in larger cohorts and investigating the biological mechanisms underlying cachexia could lead to targeted therapies.

Addressing these research directions will enable the development of more effective strategies to mitigate the impact of cancer-associated cachexia, ultimately improving patient outcomes and quality of life.

7.2 Biomarkers and Diagnostic Tools

The identification and validation of reliable biomarkers and diagnostic tools are imperative for the effective management of cancer-associated cachexia (CAC). Biomarkers play a crucial role in diagnosing, assessing progression, and evaluating therapeutic efficacy. Advances in molecular biology and imaging technologies have facilitated the discovery of potential biomarkers that reflect the pathophysiological processes underlying CAC.

Circulating microRNAs (miRNAs) have emerged as promising biomarkers due to their stability in body fluids and regulatory roles in muscle wasting and inflammation. These miRNAs offer non-invasive diagnostic capabilities, providing insights into the molecular mechanisms driving cachexia and enabling early detection and monitoring. Further validation in larger cohorts is necessary to assess their therapeutic potential.

Imaging techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI), are indispensable for evaluating muscle mass and composition in cachexia. These modalities provide detailed anatomical and functional insights, aiding in muscle wasting quantification and therapeutic assessment. The integration of advanced imaging methods, including three-dimensional numerical schemes and deep learning algorithms, enhances the accuracy and efficiency of muscle assessments.

In addition to miRNAs and imaging, metabolic and inflammatory markers have been explored as potential cachexia biomarkers. Proteomic and metabolomic analyses reveal alterations in metabolic pathways and immune responses characteristic of cachexia, paving the way for targeted diagnostic assays. Identifying specific proteins and metabolites associated with cachexia could lead to biomarker panels offering a comprehensive view of the syndrome's pathophysiology.

Developing robust diagnostic tools and biomarkers for cachexia is essential for improving patient outcomes. These tools can facilitate early intervention, guide treatment decisions, and monitor therapy responses, ultimately enhancing the quality of life for affected patients. Future research should prioritize validating these biomarkers in clinical settings and exploring novel diagnostic technologies to refine cancer-associated cachexia management.

7.3 Spatial Analysis and Imaging Techniques

Spatial analysis and imaging techniques present significant opportunities for advancing research in cancer-associated cachexia (CAC). These methodologies offer insights into the complex interactions within the tumor microenvironment (TME) and the systemic effects of cachexia on muscle and adipose tissues. Spatial analysis techniques, including first-order and second-order analyses of point processes, allow for the examination of spatial relationships between various cell types within the TME. This facilitates a detailed understanding of immune cell distribution, particularly macrophages, and how their arrangements influence tumor progression and cachexia development.

Advanced imaging modalities, such as computed tomography (CT) and magnetic resonance imaging (MRI), are crucial for assessing anatomical and functional changes associated with cachexia. These technologies provide detailed visualizations of muscle mass and composition, enabling the quantification of muscle wasting and therapeutic evaluation. Integrating advanced imaging methods, including three-dimensional numerical schemes and deep learning algorithms, enhances the accuracy and efficiency of muscle assessments, offering a comprehensive understanding of cachexia progression.

Future research should aim to develop improved models for studying CAC in humans, explore novel immunomodulatory therapies, and conduct clinical trials to validate pre-clinical findings. Refining imaging techniques and spatial analysis frameworks will be instrumental in elucidating the pathophysiological mechanisms underlying cachexia and identifying potential therapeutic targets. Leveraging these advanced methodologies will enable researchers to gain deeper insights into the spatial and temporal dynamics of cachexia, ultimately improving diagnostic and therapeutic strategies for this debilitating condition.

References

[1] Anthos Christofides, Laura Strauss, Alan Yeo, Carol Cao, Alain Charest, and Vassiliki A Boussiotis. The complex role of tumor-infiltrating macrophages. *Nature immunology*, 23(8):1148–1156, 2022.

[2] Xu Chen, Qingnan Wu, Wei Gong, Shaolong Ju, Jiawen Fan, Xiaohan Gao, Xingyang Liu, Xiao Lei, Siqi Liu, Xiangdong Ming, et al. Grp75 triggers white adipose tissue browning to promote cancer-associated cachexia. *Signal Transduction and Targeted Therapy*, 9(1):253, 2024.

[3] Lingbing Zhang and Philip D Bonomi. Immune system disorder and cancer-associated cachexia. *Cancers*, 16(9):1709, 2024.

[4] Navid Mohammad Mirzaei and Leili Shahriyari. Modeling cancer progression: An integrated workflow extending data-driven kinetic models to bio-mechanical pde models, 2023.

[5] Fengdong Cheng, Dayun Yan, Jie Chen, Zi Wang, Alex Horkowitz, Michael Keidar, and Eduardo M. Sotomayor. Enhancing innate and adaptive immune systems by cold atmospheric plasma (cap) and its antitumor immunity, 2022.

[6] Christiana M Neophytou, Myrofora Panagi, Triantafyllos Stylianopoulos, and Panagiotis Papageorgis. The role of tumor microenvironment in cancer metastasis: Molecular mechanisms and therapeutic opportunities. *Cancers*, 13(9):2053, 2021.

[7] Janina A Vaitkus and Francesco S Celi. The role of adipose tissue in cancer-associated cachexia. *Experimental Biology and Medicine*, 242(5):473–481, 2017.

[8] Peter Ghazal, Steven Watterson, Kevin Robertson, and David C Kluth. The in silico macrophage: toward a better understanding of inflammatory disease, 2011.

[9] Yuan-hui Li, Yu Zhang, Gang Pan, Li-xin Xiang, Ding-cun Luo, and Jian-zhong Shao. Occurrences and functions of ly6chi and ly6clo macrophages in health and disease. *Frontiers in Immunology*, 13:901672, 2022.

[10] Zhaojun Duan and Yunping Luo. Targeting macrophages in cancer immunotherapy. *Signal transduction and targeted therapy*, 6(1):127, 2021.

[11] Ashleigh R Poh and Matthias Ernst. Targeting macrophages in cancer: from bench to bedside. *Frontiers in oncology*, 8:49, 2018.

[12] Kajal Hamidzadeh, Stephen M Christensen, Elizabeth Dalby, Prabha Chandrasekaran, and David M Mosser. Macrophages and the recovery from acute and chronic inflammation. *Annual review of physiology*, 79(1):567–592, 2017.

[13] Zachary Reitz. The biophysical micro-environment's influence on cell fate decisions during macrophage activation and somatic cell reprogramming, 2020.

[14] Yan Fu, Trevor Glaros, Meng Zhu, Ping Wang, Zhanghan Wu, John J Tyson, Liwu Li, and Jianhua Xing. Network topologies and dynamics leading to endotoxin tolerance and priming in innate immune cells, 2012.

[15] Othman Al-Sawaf, Jakob Weiss, Marcin Skrzypski, Jie Min Lam, Takahiro Karasaki, Francisco Zambrana, Andrew C Kidd, Alexander M Frankell, Thomas BK Watkins, Carlos Martínez-Ruiz, et al. Body composition and lung cancer-associated cachexia in tracerx. *Nature medicine*, 29(4):846–858, 2023.

[16] Sara Donzelli, Alessia Farneti, Laura Marucci, Federica Ganci, Andrea Sacconi, Sabrina Strano, Giuseppe Sanguineti, and Giovanni Blandino. Non-coding rnas as putative biomarkers of cancer-associated cachexia. *Frontiers in cell and developmental biology*, 8:257, 2020.

[17] Alfonso J Cruz-Jentoft and Beatriz Montero-Errasquín. Sarcopenia. *Learning Geriatric Medicine: A Study Guide for Medical Students*, pages 99–105, 2018.

[18] Yohan Han, Hyo In Kim, and Jinbong Park. The role of natural products in the improvement of cancer-associated cachexia. *International Journal of Molecular Sciences*, 24(10):8772, 2023.

[19] Alejandro Schcolnik-Cabrera, Alma Chávez-Blanco, Guadalupe Domínguez-Gómez, and Alfonso Dueñas-González. Understanding tumor anabolism and patient catabolism in cancer-associated cachexia. *American journal of cancer research*, 7(5):1107, 2017.

[20] Othmane Laousy, Guillaume Chassagnon, Edouard Oyallon, Nikos Paragios, Marie-Pierre Revel, and Maria Vakalopoulou. Deep reinforcement learning for l3 slice localization in sarcopenia assessment, 2021.

[21] Giulio Paolucci, Isabella Cama, Cristina Campi, and Michele Piana. Three-dimensional numerical schemes for the segmentation of the psoas muscle in x-ray computed tomography images, 2023.

[22] Ayush Devkota, Manakamana Gautam, Uttam Dhakal, Suman Devkota, Gaurav Kumar Gupta, Ujjwal Nepal, Amey Dinesh Dhuru, and Aniket Kumar Singh. The interplay between physical activity, protein consumption, and sleep quality in muscle protein synthesis, 2024.

[23] Young Nam Kwon and Sung Sang Yoon. Sarcopenia: neurological point of view. *Journal of bone metabolism*, 24(2):83–89, 2017.

[24] Gökhan S Hotamisligil. Inflammation, metaflammation and immunometabolic disorders. *Nature*, 542(7640):177–185, 2017.

[25] Peijie Wu, Wei Gao, Miao Su, Edouard C Nice, Wenhui Zhang, Jie Lin, and Na Xie. Adaptive mechanisms of tumor therapy resistance driven by tumor microenvironment. *Frontiers in cell and developmental biology*, 9:641469, 2021.

[26] Jonatan A. González, Julia Wrobel, Simon Vandekar, and Paula Moraga. Analysing spatial point patterns in digital pathology: immune cells in high-grade serous ovarian carcinomas, 2023.

[27] David M Mosser, Kajal Hamidzadeh, and Ricardo Goncalves. Macrophages and the maintenance of homeostasis. *Cellular & molecular immunology*, 18(3):579–587, 2021.

[28] Mobina Tousian, Christian Solis Calero, and Julio Cesar Perez Sansalvador. Immune cells interactions in the tumor microenvironment, 2024.

[29] Mahmudul Hasan, Jakub R. Kaczmarzyk, David Paredes, Lyanne Oblein, Jaymie Oentoro, Shahira Abousamra, Michael Horowitz, Dimitris Samaras, Chao Chen, Tahsin Kurc, Kenneth R. Shroyer, and Joel Saltz. A novel framework for characterization of tumor-immune spatial relationships in tumor microenvironment, 2022.

[30] Saverio Marchi, Emma Guilbaud, Stephen WG Tait, Takahiro Yamazaki, and Lorenzo Galluzzi. Mitochondrial control of inflammation. *Nature Reviews Immunology*, 23(3):159–173, 2023.

[31] Ava J Boutilier and Sherine F Elsawa. Macrophage polarization states in the tumor microenvironment. *International journal of molecular sciences*, 22(13):6995, 2021.

[32] F Relaix, M Bencze, MJ Borok, A Der Vartanian, F Gattazzo, D Mademtzoglou, S Perez-Diaz, A Prola, PC Reyes-Fernandez, A Rotini, et al. Perspectives on skeletal muscle stem cells. *Nature communications*, 12(1):692, 2021.

[33] Stefanie K Wculek, Gillian Dunphy, Ignacio Heras-Murillo, Annalaura Mastrangelo, and David Sancho. Metabolism of tissue macrophages in homeostasis and pathology. *Cellular & molecular immunology*, 19(3):384–408, 2022.

[34] Junyi Xiong, Guojin Wu, Jinying Ning, Junlin Yan, Jian Yang, and Jinsen Kang. Neutralizing antibody against gdf15 for treatment of cancer-associated cachexia. *Plos one*, 19(8):e0309394, 2024.

[35] Mariana Janini Gomes, Paula Felippe Martinez, Luana Urbano Pagan, Ricardo Luiz Damatto, Marcelo Diacardia Mariano Cezar, Aline Regina Ruiz Lima, Katashi Okoshi, and Marina Politi Okoshi. Skeletal muscle aging: influence of oxidative stress and physical exercise. *Oncotarget*, 8(12):20428, 2017.

[36] Ewa Cendrowicz, Zuzanna Sas, Edwin Bremer, and Tomasz P Rygiel. The role of macrophages in cancer development and therapy. *Cancers*, 13(08):1946, 2021.

[37] Alberto Mantovani, Federica Marchesi, Alberto Malesci, Luigi Laghi, and Paola Allavena. Tumour-associated macrophages as treatment targets in oncology. *Nature reviews Clinical oncology*, 14(7):399–416, 2017.

[38] Yueyun Pan, Yinda Yu, Xiaojian Wang, and Ting Zhang. Tumor-associated macrophages in tumor immunity. *Frontiers in immunology*, 11:583084, 2020.

[39] Elvira Mass, Falk Nimmerjahn, Katrin Kierdorf, and Andreas Schlitzer. Tissue-specific macrophages: how they develop and choreograph tissue biology. *Nature Reviews Immunology*, 23(9):563–579, 2023.

[40] Alan D. Rendall. Analysis of a mathematical model for interactions between t cells and macrophages, 2010.

[41] Alberto Mantovani, Paola Allavena, Federica Marchesi, and Cecilia Garlanda. Macrophages as tools and targets in cancer therapy. *Nature Reviews Drug Discovery*, 21(11):799–820, 2022.

[42] Bernadette J. Stolz, Jagdeep Dhesi, Joshua A. Bull, Heather A. Harrington, Helen M. Byrne, and Iris H. R. Yoon. Relational persistent homology for multispecies data with application to the tumor microenvironment, 2023.

[43] Shanze Chen, Abdullah FUH Saeed, Quan Liu, Qiong Jiang, Haizhao Xu, Gary Guishan Xiao, Lang Rao, and Yanhong Duo. Macrophages in immunoregulation and therapeutics. *Signal transduction and targeted therapy*, 8(1):207, 2023.

[44] Alan D. Rendall. Multiple steady states in a mathematical model for interactions between t cells and macrophages, 2011.

[45] Siamon Gordon and Annette Plüddemann. Tissue macrophages: heterogeneity and functions. *BMC biology*, 15(1):53, 2017.

[46] Greg Lemke. How macrophages deal with death. *Nature Reviews Immunology*, 19(9):539–549, 2019.

[47] Rachel McCormick and Aphrodite Vasilaki. Age-related changes in skeletal muscle: changes to life-style as a therapy. *Biogerontology*, 19(6):519–536, 2018.

[48] Giulia Giantesio and Alessandro Musesti. A continuum model of skeletal muscle tissue with loss of activation, 2017.

[49] Vito Chianca, Domenico Albano, Carmelo Messina, Salvatore Gitto, Gaetano Ruffo, Salvatore Guarino, Filippo Del Grande, and Luca Maria Sconfienza. Sarcopenia: imaging assessment and clinical application. *Abdominal Radiology*, 47(9):3205–3216, 2022.

[50] Chang-Hoon Lee and Eun Young Choi. Macrophages and inflammation. *Journal of Rheumatic Diseases*, 25(1):11–18, 2018.

[51] Paolo Tieri, Silvana Valensin, Vito Latora, Gastone C. Castellani, Massimo Marchiori, Daniel Remondini, and Claudio Franceschi. Quantifying the relevance of different mediators in the human immune cell network, 2004.

[52] Sarah Triboulet, Catherine Aude-Garcia, Lucie Armand, Adèle Gerdil, Hélène Diemer, Fabienne Proamer, Véronique Collin-Faure, Aurélie Habert, Jean-Marc Strub, Daniel Hanau, Nathalie Herlin, Marie Carrière, Alain Van Dorsselaer, and Thierry Rabilloud. Analysis of cellular responses of macrophages to zinc ions and zinc oxide nanoparticles: a combined targeted and proteomic approach, 2014.

[53] Ruoxin Fang, Ling Yan, and Zhengkai Liao. Abnormal lipid metabolism in cancer-associated cachexia and potential therapy strategy. *Frontiers in Oncology*, 13:1123567, 2023.

[54] Mireille Chevallet, Hélène Diemer, Alain van Dorsselaer, Christian Villiers, and Thierry Rabilloud. Toward a better analysis of secreted proteins: the example of the myeloid cells secretome, 2007.

[55] Alyssa Imbert, Nathalie Vialaneix, Julien Marquis, Julie Vion, Aline Charpagne, Sylviane Metairon, Claire Laurens, Cedric Moro, Nathalie Boulet, Ondine Walter, Grégory Lefebvre, Jörg Hager, Dominique Langin, Wim Saris, Arne Astrup, Nathalie Viguerie, and Armand Valsesia. Network analyses reveal negative link between changes in adipose tissue gdf15 and bmi during dietary-induced weight loss, 2022.

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