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The Role of Clinical Immunology in Non-Communicable Chronic Diseases: Pathophysiological Insights and Immunotherapeutic Perspectives

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ABSTRACT: Common NCDs, such as type 2 diabetes, cardiovascular disease, cancer and obesity have become increasingly prevalent in populations worldwide. These are complex issues in relation to the underlying mechanisms of public health and involvement of immune system. The relevance of clinical immunity in the development and/or course of these diseases appears to be even more evident when considering shared inflammatory and immune pathways, including those involved in renal failure or removal; recently developed immunotherapies. This review emphasizes three main concepts: the impact of the immune system on clinical physiology, how immune dysregulation leads to a select set of chronic diseases and extrinsic factors (foods, pollutants, lifestyle habits-of-mind) that modulate immunity. It also reviews new immunotherapeutic strategies such as anti-cytokine development, checkpoint inhibitor therapy, regulatory-cell-based approaches and nanotechnology-based interventions, and microbiota-targeted therapies. The studies highlight the importance of transitioning from traditional treatment approaches to one that is immune-focused, precision-based and personalized—to be guided by a comprehensive understanding of the immune interactions in individual patients' diseases. The paper ends with suggestions for pragmatic steps, including promoting interdisciplinary research, stimulants for therapeutic innovation and identifying immune biomarkers for early detection, that could optimally improve the patient's outcome.

Keywords: Clinical Immunology, Chronic Non-Communicable Diseases, Cytokines, Immune Dysfunction, Immunotherapies, Precision Medicine

1. INTRODUCTION

NCDs constitute the dominant share of global illness and death at present contributing to nearly 71% of all mortality worldwide [1]. They are of long duration and multifactorial cause, and impose heavy burdens on both medical systems and national economies. The most common are cardiovascular diseases (CVD), type 2 diabetes mellitus, chronic respiratory diseases including asthma and COPD and cancer [2].

Traditionally, the etiology of NCDs was predominantly attributed to genetic predispositions and other metabolic susceptibilities and exposure to environmental and lifestyle risk factors such as unhealthy dietary pattern, smoking, poor physical activity [3].

Although vascular endothelial dysfunction are still the central concept of disease pathogenesis, many recent immunological progresses have implicated that both systemic and local immune abnormalities contribute to the initiation, progression and complications of these disorders [4].

Clinical immunology provides a window into the immune system's healthy activity, as well as its maladaptive behavior in chronic disease. Chronic, low-grade inflammation mediated by prolonged activation of innate immunity and dysregulated adaptive immune responses are hallmark features associated with various NCDs [5].

Major mediators, such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and interleukin-1β (IL-1β) and cells types such as macrophages, T lymphocytes and dendritic cells, play a significant role in pro-inflammatory response that further drives tissue damage/organ failure [6]. In type 2 diabetes, an inflammatory signal disrupts insulin signaling and results in insulin resistance and β-cells damage [7].

Similarly, atherosclerosis, the predominant pathological cause underlying cardiovascular disease (CVD), is also currently considered an immune-mediated disorder in which immune infiltrates within blood vessel walls are promoting growth and destabilization of plaques [8].

In the case of respiratory diseases, immune dysregulation is clearly observed in asthma, and this skewing toward Th2 responses and eosinophil-mediated inflammation contributes to airway hyperreactivity and structural remodeling [9].

The tumor environment in most of the cancers, is manipulated from evasion and immune-editing, that create conditions favorable to survival and proliferation of malignant cells following the escape mechanisms from therapeutic interventions [10].Immune pathways are also highly intertwined with genetic, epigenetic, metabolic and environmental determinants that together mold susceptibility and clinical evolution beyond what has simply been described with categories of responses [11].

Obesity, for example, is a well-studied condition in which chronic inflammation contributes to the accumulation of immune cells within adipose tissue that exacerbates metabolic dysfunction and cardiovascular risk [12]. Stressed and environmental pollutants contribute to immune modulation, which is a part of progression and severity [13].

New therapeutic approaches have emerged from these immunological breakthroughs, leading to the development of innovative immunotherapies with the promise of restoring aberrant immune responses in NCDs. Examples include cytokine-targeted biologics, immune checkpoint blockade, and therapeutic vaccines for restoration of tolerance or augmentation of protective immunity [14,15].

The development of clinical immunology and its translation into the clinic therefore represent a strong potential for enhancing therapies and clinical response. Citation 2: Functional Definition of B-cell-rich/MZ/GC MALT structures as explored by gene expression analysis at the single cell level.

The objective of this review is to offer an extensive and critical vision about the state of art today in the knowledge of experimental or clinical immunology involvement in non-communicable chronic diseases, explaining immune pathophysiology mechanisms while discussing entirely new perspectives for immunotherapeutics approaches in current or forthcoming therapeutics.

The commentary also describes current research needs, and suggests areas of focus for future research on potential contributions of immunology to the multidisciplinary basis for NCD control.

2. CLINICAL IMMUNE SYSTEM

The human immune system is a complex and dynamic ecosystem that maintains organismal homeostasis and protects against infectious pathogens, malignancies, and other injurious substances.

It may be conceptually separated into two intertwined arms, namely: the innate immune system and acquired or adaptive immune responses [16].

The nonspecific, rapid responses that characterize the initial response are features of the innate immune system; these are immunity's first line of defense consisting primarily of physical barriers (eg, skin, mucosal surfaces), cellular elements (eg macrophages, neutrophils, dendritic cells [DCs], natural killer [NK] cells), and soluble mediators (called lumoral factors) such as components of complement and cytokines.

Nate immune cells recognize pattern recognition receptors (PRRs), including Toll-like receptors (TLRs), PAMPs: conserved molecular patterns in pathogens. Upon recognition of these PAMPs, intracellular signaling pathways are activated to promote the production of pro-inflammatory cytokines and chemokines and recruit other immune cells and activate the adaptive immune response [17, 18].

In addition to protecting against infections, innate immunity also serves as a sensor of tissue damage and inducer of repair processes, but can cause chronic inflammation and tissue injury if responses are dysregulated, as seen in non-communicable chronic diseases [19].

The adaptive immune system supplies antigen specific responses and immunological memory, mediated by T as well as B lymphocytes. T cells can be categorized into distinct subpopulations: the CD4+ helper T cells, which coordinate immune reactions through cytokine release and the CD8+ cytotoxic T cells, which lyse infected or transformed cells.

B cells also aid by producing pathogen-specific antibodies vital for neutralizing pathogens and clearing them [20].

Adaptation of the immune response to distinct insults is fine-tuned by crosstalk between adaptive immunity and immune reactions driven by incognoscible signals.

Crucially, immune regulation is under strict control by factors like regulatory T cells (Tregs), anti-inflammatory cytokines (i.e. interleukin-10) and immune checkpoint molecules (e.g., PD-1, CTLA-4) that restrain indiscriminate proliferation of immune responses and autoimmunity [21].

Impairment to these regulatory mechanisms may be involved in the pathological chronic inflammation and immune dysregulation seen in several NCDs.

For some non-communicable chronic diseases, both innate and adaptive immunity participate in pathogenesis. r example, in obesity, adipose tissue macrophages frequently adopt pro-inflammatory phenotypes, which leads to insulin resistance and type 2 diabetes pathogenesis [22].

Likewise, T helper cell subsets, including Th1 and Th17 cells as well as subsets of Th (T helper) peripheral blood cells are strongly related to the role that persistent inflammation has in both autoimmune-like presentations of some chronic disease states and atherogenic mechanisms for atherosclerosis [23].

Cytokine pathways, in particular tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and interleukin-1β (IL-1β), play a central role as mediators of inflammation and tissue remodeling [24].

The importance of an interrelationship between the innate and adaptive immune systems is underscored by recent findings showing that systemic immunity, risk, and trajectory for chronic disease are significantly affected by the gut microbiota [25].

Moreover, epigenetic changes and metabolic reprogramming in immune cells contribute to the complex network of immune regulation under these conditions [26].

The detailed knowledge of those immune mechanisms and their regulation is therefore essential to generate immunotherapies targeting the re-establishment of immune homeostasis, as well as preventing further progression towards clinical symptomatic stages, see figure (1), figure (2).

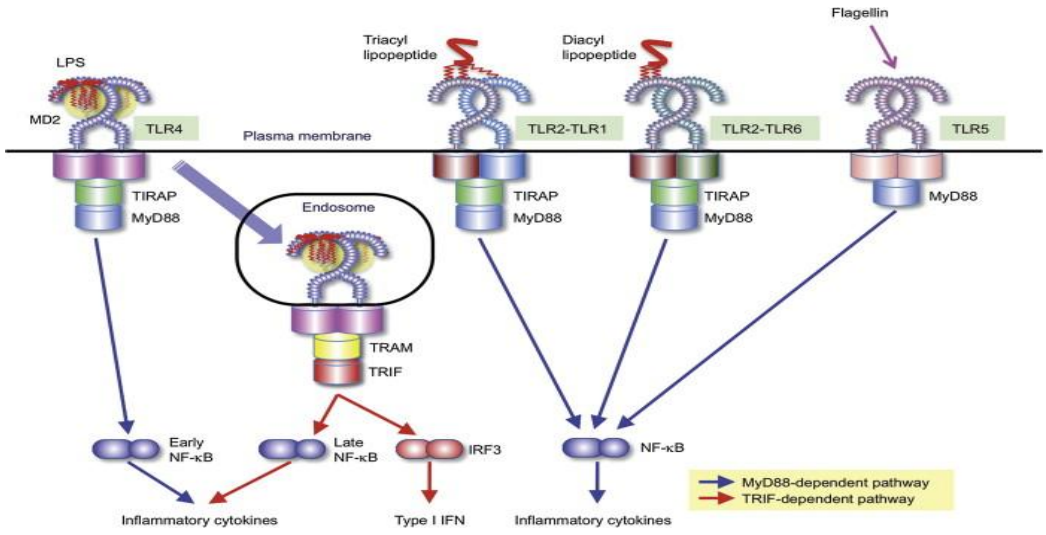

FIGURE 1. - PAMP recognition by cell surface TLR.

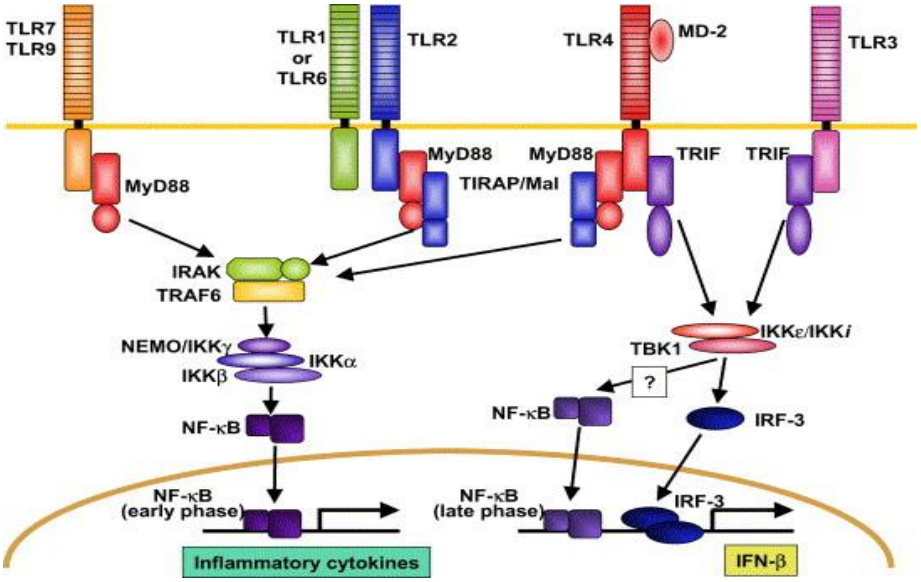

FIGURE2. - Overview of TLR signaling pathways.

2.1 ROLE POF THE IMMUNE SYSTEM IN SPECIFIC NON-COMMUNICABLE CHRONIC DISEASA

The immune system plays a multifaceted and disease-specific role in the pathophysiology of non-communicable chronic diseases (NCDs), where immune dysregulation contributes both to disease onset and progression. Understanding these mechanisms is crucial for identifying immune-related therapeutic targets.

2.2 TYPE 2 DIABETES MELLITUS (T2DM)

A pathological feature of T2DM that is a consequence of obesity is chronic low-grade inflammation, in which innate immune cells including adipose tissue macrophages (ATMs) infiltrate visceral fat and release pro-inflammatory cytokines (e.g., TNF-α, IL-6) that disrupt insulin signaling leading to insulin resistance [27].

Adaptive immunity also contributes through Th1 and th17 cell activity amplifying local inflammation and β-cell apoptosis [28].

2.3 CARDIOVASCULAR DISSEASE (CVD)

Atherosclerosis, the basis for most CVDs, is now regarded as an immunological chronic inflammatory insult [29]. Altered lipoproteins, including oxidized LDL, are endocytosed by macrophages to create foam cells and induce cytokine networks which lead to plaque development and vulnerability.

T cells are also involved in the pathogenesis being the source of interferon-γ and drivers of vascular inflammation [30].

2.4 CHRONIC RESPIRATORY DISEAES

Immunologically, asthma and COPD are distinct but overlapping diseases. Asthma generally is driven by Th2-mediated eosinophilic inflammation and COPD is characterized by neutrophilic inflammation, with release of proteases/ ROS from innate immune cells that promote tissue destruction [31].

Chronic activation of the airway immune cells also participates in the remodeling and functional impairment of the airways in both diseases [32].

2.5 CANCER

The immune system can paradoxically both eliminate and promote the growth of tumors. The dual nature of host immunity in colorectal cancer is exemplified by the process of immunoediting, comprising three stages or 'E's: elimination, equilibrium and escape [33].

Although the immune response allowed cytotoxic T lymphocytes and NK cells kill of transformed cells, tumors generally escape (the) immunity through expression of immune checkpoints molecules and recruitment of regulatory cells [34].

3. FACTORS INFLUENCING IMMUNE HOMESTASIS IN NCDS

Maintaining immune homeostasis is vital for preventing chronic inflammation and disease progression. Several intrinsic and extrinsic factors can disrupt this balance.

3.1GENETIC AND EPIGENETIC FACTORS

Genetic polymorphisms in cytokine genes (e.g., TNF-α, IL-1β) and PRRs (e.g., TLR4) can influence immune responsiveness and susceptibility to inflammation-driven diseases [35].

Additionally, epigenetic modifications such as DNA methylation and histone acetylation in immune cells alter gene expression patterns and contribute to long-term immune reprogramming [36].

3.2 METABOLIC AND NUTRITIONAL STATUS

The hypertrophy, hypoxia and adipocyte-secreted adipocytokines, such as leptin and resistin in obesity/metabolic syndrome are all associated with systemic inflammation [37].

These categories also promote skewing of macrophage polarization towards the pro-inflammatory M1 phenotype and the disruption of endogenous regulatory immune loops [38].

Omega-3 fatty acids and vitamin D, on the contrary, have immunomodulatory properties and promote a downregulation of inflammation [39].

3.3 MICROBIOTA -IMMUNE INTERACTIONS

The immune system development and regulation are strongly influenced by the gut microbiota. Alterations of the microbial composition, referred to as dysbiosis, have been associated with increased intestinal permeability, systemic exposure to endotoxin and sustained immune stimulation [40].

Commensal microorganisms-derived metabolites especially, short-chain fatty acids (SCFAs) play an essential role in controlling T helper cell differentiation and immune tolerance pathways [37–39].

Disrupted SCFA has been linked to diseases including diabetes, CVD and autoimmune diseases [41].

3.4 PSYCHOSOCIAL AND ENVIRONEMTAL STRESSORS

Exposures such as fine particulate matter (PM2. 5), tobacco smoke and heavy metals can activate the innate immune response and cause oxidative stress,both of which lead to increased inflammation [42].

Concurrently, psychosocial stress alters immune response through neuroendocrine–immune crosstalks and could modulate NLP activity in a manner that enables the body to become more susceptible to chronic inflammatory conditions [43].

4. DISCUSSION

This review underscores immune dysfunction as a common underlying mechanism of the NCD pathogenesis. Chronic low-grade inflammation, sustained by maladaptive innate and adaptive immune responses, appears as a commonality in metabolic, cardiovascular, respiratory diseases as well as in cancer with adverse effects on disease progression and tissue destruction.

In metabolic and vascular dysfunctions, activation of the innate immune response particularly macrophage polarization and pattern recognition receptors signaling has been implicated as a common mechanism.

Pro-inflammatory macrophages arrest insulin transduction in obesity and type 2 diabetes, whereas immune-driven lipid deposition and cytokine production during atherosclerosis enhance plaque formation and rupture. These results lend further support to the proposition that the major NCDs are – in part – immune-based conditions.

Dysregulation of adaptive immunity further augments chronic inflammation as an aggressive effector T cell response combined with inadequate regulation promotes prolonged tissue damage. The same immune dysregulation drives immune escape through checkpoint pathways and immunosuppressive microenvironments in cancer, highlighting the context-dependence of immunity in disease.

Crucially, immune homeostasis is regulated by external factors such as nutrition, composition of the microbiota, environmental exposure and psychosocial stress that cumulatively shape immune activation and tolerance.

Novel immunotherapies including targeting cytokines, immune checkpoints, regulatory cells and microbiota–immune interactions represent potential precision approaches for NCD management.

However, a careful patient stratification and prolong safety assessment are needed for successful therapeutic translation.

5. CONCLUSION

Complex interplay between the immune system and non-communicable diseases (NCDs), especially chronic ones has become a fast growing sphere of scientific interest, indicating that the way in which diseases initiate and progress, and diagnostic tools as well as treatment options need to be altered.

A wealth of evidence now exists to support that immune dysregulation—either too much inflammation or not enough regulation—is a key component in the development and progression of T2D, CVDs, obesity, NAFLD and several other types of.

Progress in clinical immunology is changing therapeutic paradigms from symptom-relief strategies onto the causes of immune disruption.

Emerging immunomodulatory approaches targeting cytokine inhibition, checkpoints, regulatory immune cell (RIC) therapies, gut microbiome interventions, and nanotech-driven design strategies have all demonstrated striking preclinical proof-of-principle and in some instances clinical efficacy Nevertheless, implementation as standard-of-care still faces the challenge of patient heterogeneity,l ong-term safety considerations, the trade-off between therapeutic benefit versus potential toxicities.

From a perspective of the future, the fusion between immunobiology and genetic, environmental and clinical profiling provides the foundation for genuine personalized.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest

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