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Shared Pathways Between Ankylosing Spondylitis and Cardiovascular Disease: A Systems Biology Approach

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ABSTRACT

Ankylosing spondylitis (AS) is a chronic inflammatory disease primarily affecting the axial skeleton, with patients exhibiting a significantly elevated risk of cardiovascular disease (CVD)[1]. This review explores the shared pathways between AS and CVD through a systems biology approach, integrating multi-omics data to uncover common molecular mechanisms such as inflammation, immune dysregulation, and metabolic disturbances[2]. Key findings highlight the role of endothelial dysfunction, genetic factors such as HLA-B27, and environmental influences such as gut microbiota in linking these conditions [3]. Systems biology tools, including network analysis and pathway enrichment, reveal potential therapeutic targets like TNF-α inhibitors and statins for dual disease management[4]. The study underscores the need for further experimental validation to translate these insights into clinical applications, offering new avenues for risk assessment and personalized treatment strategies[5].

Keywords: Ankylosing spondylitis, Cardiovascular disease, Systems biology, Inflammation, Endothelial dysfunction

1. Introduction

Ankylosing spondylitis (AS) is an inflammatory disease that primarily affects the spine. It can also result in chronic pain and limited mobility of the affected joint, leading to significant disability [6]. Patients suffering from AS had a two times greater risk of developing cardiovascular disease (CVD) as a complication compared with the general population [7]. This lives a burning question about common mechanisms underlying AS and CVD. Recent progress in systems biology offers unprecedented means to analyze cooperate endeavors and connectedness of diverse systems. Consequently, it holds great promise to better unravel the shared pathways supported by nature and actions between these diseases [8]. Approaches to tackle this analysis included identification of representative system level dissimilarity and gene enrichment analysis, affinity propagation clustering, weighted gene co-expression network analysis and permutation tests. Local perturbation and transition network were derived for molecular reaction graph of selected pathways in the infection metabolism to extend the analysis into a systems-wide view of competing and cooperating actions of these pathways [9]. Shared pathways provided new opportunities for drug repositioning. REST that negatively regulated both AS and CVD was pro-inflammatory of arthritis in a model [10]. Using original R software packages of the above analysis, the relevant libraries were needed as well, especially those for area under the ROC curve (AUC) rankings on the basis of combined subgraphs and enrichment analysis [11]. These shared pathways between diseases implicated it remained a bitter pill for millions of patients. Attention was also drawn on the robustness, generalizability and extensibility of the aims and procedures of this analysis [12]. The highlighted motifs of shared pathways hold great promises to advance the understanding of crosstalk between disease mechanisms and develop new strategies for drug repositioning. DRD1 may be safely repurposed for both diseases, while REST is a potential novel candidate. Further experimental validation and in vivo testing of the highlighted pathways was warranted. Recent progress in systems biology provide unprecedented means to analyze the cooperate endeavors and connectedness of diverse systems. Consequently, it holds great promise to better unravel the shared pathways supported by nature and actions underlying AS and CVD. Shared cellular and genomic pathways may account for the high prevalence of CVD in patients suffering AS disease. There were many common and novel pathways shared by AS and CVD. Exploration of the responses of these shared pathways on diverse initiation events may yield new insights into the understanding of the crosstalk between diseases and inform new strategies for drug repositioning and therapeutic management.

2. Rationale and Context

Ankylosing spondylitis (AS) is a chronic inflammatory disease associated with accelerated atherosclerosis and increased morbidity and mortality from cardiovascular disease (CVD) compared to the general population [13]. While traditional cardiovascular risk factors play a role, a combination of profoundly enhanced non-traditional risk associated with systemic inflammation and autoimmune phenomena, along with the uncertain effects of contemporary treatments, is thought to contribute. These processes are under intense investigation, yet much remains to be elucidated regarding the upstream mechanisms and mediators driving the increased risk. AS is characterized by inflammation of the enthesis, with primary involvement of the spine throughout the disease course. It is more prevalent in HLA-B27–positive men, for reasons that remain unclear. Joints with both synovium and enthesis involvement share similar pathoanatomic changes and a common inflammation-initiating process. However, inflammation originating at the enthesis may extend to the adjacent synovium, leading to synovitis of the spine that often remains overlooked for years [14]. This shared pathogenesis may also explain common complications, such as accelerated CVD, though the exact mechanisms have yet to be fully clarified. As such, the convergence of processes and dysregulations—at least at the transcriptome and proteome levels—in AS and CVD was evaluated as a starting point for a broader investigation into disease networks, the propagation of dysregulations mediating shared downstream processes, and the potential for identifying targetable common pathways. A small but significant overlap of inflammation-driven upstream cytokine-regulatory coaction was revealed at the secretome proteome level, and more globally with numerous strong upstream drivers acting multiplicatively at the transcriptome–proteome levels. Consequently, a convergence of pre-atherogenic dysfunction in endothelial and vascular smooth muscle cells, together with dysregulation of hemostatic mechanisms and the production of an array of pro-inflammatory mediators controlling their activity, was identified.

2.1. OVERVIEW OF ANKYLOSING SPONDYLITIS

Ankylosing spondylitis (AS) is an inflammatory rheumatic disease from the group of spondyloarthritis that primarily affects the axial skeleton [15]. AS mainly affects the sacroiliac joints and the vertebral column, leading to pathological new bone formation resulting in ankylosis. Pathological changes lead to back pain which contributes to an increased risk of work disability and impairment in the quality of life. It is a chronic inflammatory disease and has extra-articular manifestations on various organ systems. The precise pathogenesis of AS is still unknown, but genetic factors, in particular, HLA-B27 and infections, particularly with Klebsiella pneumoniae, are of great importance. Cardiovascular disease (CVD) is a complication of AS that significantly affects the prognosis of patients. CVD in patients with AS is associated with premature mortality. The introduction of biological treatment has improved the outcome in patients with AS concerning the musculoskeletal system but the effect of treatment on the risk of CVD in patients with AS is still uncertain. There is growing evidence that systemic inflammation leads to atherosclerosis and enhances the cardiovascular risk in patients with inflammatory diseases [16]. The systemic inflammation may lead to accelerated atherosclerosis via multiple pathways such as endothelial dysfunction, inflammation and cytokines, and increased levels of traditional risk factors. Endothelial dysfunction is associated with an increased risk of CVD and has been observed in patients with AS. This could contribute to an increased cardiovascular risk in these patients. The

understanding of the mechanisms and mediators of the increased non-traditional risk associated with AS is still limited and better understanding of this association is required. The endothelium is suggested to represent an initial step in the pathogenesis and maintenance of all stages of atherogenesis. Endothelial dysfunction leads to increased permeability which allows the entry of lipoprotein particles to the arterial wall [17].

2.2. OVERVIEW OF CARDIOVASCULAR DISEASE

Cardiovascular diseases (CVDs) consist of various heterogeneous disorders that affect the heart, vasculature, or structure leading to accelerated morbidity and mortality. CVDs can be categorized into four main types: coronary artery disease, cerebrovascular disease, peripheral arterial disease, and aortic disease, which may all originate from atherosclerosis and lead to ischemia in the heart; however, other causes such as congenital abnormalities, infection, or hypertrophies are also possible. Underlying the aforementioned diseases is a broad pathology of the main risk factors that promote and accelerate the natural course of the disease such as hyperlipidemia, hyperglycemia, smoking, and hypertension. They all induce local inflammation along with competing macrophages behaving actively (proinflammatory) or passively (anti-inflammatory). This inflammation sets up atherogenic processes in the arterial walls and promotes the phenomena of plaque rupture leading to subsequent thrombosis and occlusion of arteries. Plaques may linger within arterial walls for long periods but could also grow to advance rupture and occlusion [18]. Ankylosing spondylitis (AS) is a chronic inflammatory autoimmune disorder primarily affecting the spine and peripheral joints, leading to significant mobility limitations. Patients exhibit a range of manifestations including low back and buttock pain, stiffness in the early morning and after prolonged inactivity, and swollen joints. Synovitis, enthesitis, and dactylitis may compromise the quality of life. The incurable disease course frequently ends with an ankylosis and is associated with a greater risk of systemic diseases such as osteoporosis, inflammatory bowel disease, and CVD. Cardiovascular disease further contributes to an increased mortality risk in patients with AS. CVD is a broad descriptor of a range of symptoms and disorders that affect the heart, blood vessels, or structure. There are many types of CVDs but they can be broadly grouped into valvular heart disease, coronary artery disease, arrhythmia, congenital conditions, cardiomyopathy, peripheral artery disease, or pulmonary vascular disease [19].

2.3. EPIDEMIOLOGY OF COMORBIDITIES

Ankylosing spondylitis (AS) is a chronic inflammatory disease that primarily affects the axial skeleton and can result in permanent structural damage and impaired function. Although the main cause of AS has not yet been determined, it is known that genetic, environmental, and immunological factors contribute to its pathogenesis. In addition to the axial skeleton, the peripheral joints, eye, heart, and skin may also be affected. Patients with AS complain of many concerns during the disease journey. Apart from the cardinal signs of sacroiliitis and spondylitis, peripheral arthritis, enthesitis, and extra-articular manifestations affecting the eye, heart, lung, and skin may be observed [20]. Many extra-articular manifestations are found to potentially affect health-related quality of life (HRQOL), as measured using generic, disease-specific, and utilization index-derived instruments. One of the most important extra-articular manifestations of AS that may affect HRQOL and survival is cardiovascular disease. Cardiovascular events are found to be associated with a higher prevalence of all-cause and cardiovascular mortality in patients with AS compared with healthy individuals. It is also exhibited that patients with AS have increased incidence rates of cardiovascular events, including cerebrovascular stroke, myocardial infarction, and heart failure. Presence of major adverse cardiovascular events was positively correlated with disease duration. The main processes associated with cardiovascular disease observed in patients with AS include (1) Traditional cardiovascular risk factors that are expected to detect cardiovascular events in the general population, including older age, male sex, current smoking, cholesterol, diabetes mellitus, and blood pressure, which take part in both the pathogenesis of atherosclerosis and arteriosclerosis. (2) Non-traditional cardiovascular risk factors in AS consist of AS itself, high disease activity with objective findings including elevated C-reactive protein, imaging findings at either the spine or hip joint, and the presence of syndesmophytes on lateral radiography and simplified enthesitis scores, since studies have depicted that a high level of disease activity is associated with an increased burden of cardiovascular diseases. In other words, apart from traditional cardiovascular risk factors, AS itself and high disease activity state are considered non-traditional risk factors for cardiovascular disease [21].

3. Pathophysiology

Human studies provide valuable information about mechanisms linking AS to CVD. Some studies focused on common traditional CVD risk factors to account for the increased probability of disease. A meta-analysis revealed that the accumulation of CVD risk factors was greater in AS patients than controls, although traditional CVD risk factors explained only a small percentage of increased CVD risk found in AS patients compared to the general population. Other studies focused on non-traditional CVD risk factors and revealed associations between biomarkers of inflammation, diffuse coronary artery disease in angiography, and CVD events including myocardial infarction, heart failure, stroke, and sudden cardiac death. Additionally, the presence of one common feature in atherosclerosis and AS – an abnormal immune response – led to speculation about possible shared pathways such as inflammation or alteration of lipid metabolism. The majority of evidence linking AS to CVD is epidemiological. A study examining common dietary intake in a cohort of AS patients and controls found that a higher intake of saturated, trans, and total fat was associated with an increased risk of both AS and CVD, although no association between abundant aquatic products or omega-3 consumption and the presence of CVD was found. However, retrospective design, recall bias, and lack of validation using other methods to estimate usual dietary intake limited the conclusions that could be drawn from the study. Another population-based study found that women with AS were at a lower risk of heart failure compared with controls. Examination

of left ventricular structures and function revealed no significant difference in left ventricular volume and mass index or low/neither blood pressure group prevalence between AS patients and controls. However, abnormal diastolic function was suggested in middle-aged AS patients compared with counterparts without AS, although the difference was insignificant.

3.1. INFLAMMATORY MECHANISMS

Spondyloarthritis (SpA) is a type of inflammatory arthritis that has a major impact on the ability of patients to perform daily activities and is associated with a significant reduction in work productivity. Typical SpA include ankylosing spondyloarthritis (AS), non-radiographic axial SpA, psoriatic arthritis, and inflammatory bowel disease-associated arthritis. One of the most serious long-term complications in these patients is the increased risk for premature cardiovascular disease (CVD). Conventional cardiovascular risk factors do play a role, but underlying inflammation may also have an important role. During recent years there has been an increasing interest in the shared pathways between SpA and CVD, but very little is known about the actual biological processes by which disease entities interact. There is a long-standing interest in the role of inflammation in atherosclerosis/cardiovascular disease (AS/CVD), but it is unclear where inflammatory pathways first activate, and whether local inflammation can indirectly affect other tissues/organs elsewhere [22]. Shared pathways between inflammation and vascular dysfunction in AS/CVD have been investigated and discussed. It is suggested that both local (vascular) and systemic inflammation play a role in the development of AS and both AS and CVD. The local inflammation may generate inflammatory agents that cause vascular dysfunction. This vascular dysfunction in turn may cause systemic inflammatory activation, which in turn contributes to the further development and persistence of both diseases. On the other hand, the systemic immune response is involved as well. Systemic inflammation may additionally cause the pro-inflammatory autoantibody response in both diseases. More generally, it is suggested that there are disease-independent mechanisms that contribute to the much-observed association between chronic inflammation and increased CVD risk. So far these disease-independent processes are largely not understood. In this research, with the final goal to understand disease-independent pathways, purely cardiometabolic processes are studied first to gain better insight into the biology of AS. Shared pathways have been shown between AS and a large number of other conditions. This is interesting from a biological perspective. However, strictly speaking, pathways that take place outside the realm of AS cannot be considered shared pathways [23].

3.2. ENVIRONMENTAL INFLUENCES

In addition to genetic risk factors, environmental influences are thought to also play a role in the development of AXSPA and CVD. Although environmental factors have recently been recognized as a potential contributor to the pathogenesis of AXSPA, only a few factors have been specifically examined and evaluated. In addition to the antigenic exposure to HLA-B*27, which is well established for its role in AXSPA pathogenesis, more recently, cigarette smoking has been reported in association with an increased risk of AXSPA. Recently, several studies have suggested that exposure to metals, which was assessed indirectly through the use of urine specimen analysis, may be associated with AS. Although not all studies demonstrated a significant relationship, a trend towards increasing odds was suggested for aluminum, antimony, cadmium, and tungsten. Additional research on the influence of inorganic dust exposure on AS development, which to date has only been investigated in relatively small studies, is warranted. The possibility of such an association is supported by recent findings that suggested elevated urine concentrations of heavy metals, including arsenic, gold, and several isotopes of lanthanide, in AS patients, and of platinum, strontium, titanium, and uranium in AS patients with more severe disease. Other environmental factors of interest are infectious agents, particularly Klebsiella pneumoniae [24]. The role of the gut microbiota in AS has been actively investigated and it is believed that dysbiosis of the gut microbiota might affect association with HLA-B27 molecule and ACC which lead to adjacent segmental abnormality. In addition to its effect on disease behavior itself, there is increasing evidence that gut microbiota alterations are associated with metabolic syndrome, which is commonly observed in AS population and may alter atherosclerosis process. Nevertheless, firm evidence for a distinct gut microbiota signature in AS has not been observed, which warrants further future studies to examine the complexity and stability of gut microbiota in the context of AS and to elucidate the role of gut microbiota alterations in comorbidities of AS. Given the pro-inflammatory milieu in AS patients, the immune system, and metabolism may be predominantly altered, and large, longitudinal studies are needed to investigate these aspects in the future. Some studies observed that the extent and severity of CVD, including aortic stiffness and IMT in AS population, may be positively associated with disease activity. These observations are supported by a prior study, wherein dysregulation of miRNAs involved in pro-inflammatory, pro-thrombotic and lipid metabolism pathways were identified in AS population with more severe disease, as compared to those with milder disease. Moreover, it has been proposed that hyperlipidemia pertaining to elevated triglyceride level may contribute to the severity of AS [25].

4. Systems Biology Framework

Emerging evidence suggests a shared pathophysiology between ankylosing spondylitis (AS) and cardiovascular disease (CVD), triggering a stronger interest to study the overlapping signaling pathways between the two diseases. Since it is still ambiguous how the interactions between nodes in the molecular network led to different clinical manifestation states in AS and CVD, a systems biology approach has been conceived to induce a global view of the complex interaction network enveloping AS and CVD. For this purpose, a whole network was constructed by the integration of the key nodes and their direct interactions in AS and CVD molecular networks, and the interacting proteins/protein complexes were well dispersed using a modularization algorithm called MCODE. Subsequently, the two states of the interaction network were modeled with the corresponding

differential pathways enriched in each state, which shed light on how the common pathways may give rise to different clinical manifestations in AS and CVD. Overall, the potential utility of systems biology approach to explore common or different molecular pathways between diseases, and to uncover the underlying mechanisms. AS is a complex rheumatic disease that mainly affects the axial skeleton and is closely associated with CVD. Increasing evidence suggests that inflammation in AS might be involved in the development of endothelial dysfunction and subsequently accelerate atherogenesis, leading to an increased CVD risk. Although many functional experimental studies have been performed to explain how the molecules interact with each other in each individual disease, it remains to be uncertain how they fare against each other and what happens at the systems level. Therefore, the shared and distinct pathways between AS and CVD were explored with respective pathway networks, and a systems biology approach was introduced. The results suggested that both AS and CVD share similar inflammatory pathways to relative RA and MI, and complex interactions between the shared pathways give rise to different clinical manifestations between AS and CVD.

4.1. INTRODUCTION TO SYSTEMS BIOLOGY

The systems biology approach aims at elucidating the shared molecular pathways between ankylosing spondylitis (AS) and CVD. As a data-driven methodology to infer unexpected relationships among molecules and unreported paths linking genes to diseases, systems biology utilizes hypotheses-generating methodologies. These methodologies encompass the bottom-up, top-down, and reverse-complement approaches. For instance, the bottom-up approach has been utilized to retrieve genes to construct interaction networks or to identify shared regulator nodes. Conversely, the top-down approach generally begins with a 'therapeutic goal,' bruit's spatial and temporal influence upon which proteins, genes, pathways, or biologic networks will facilitate or compromise responses, ultimately leading to drug and therapeutic studies [26]. During the last decade, the widespread availability of high-throughput 'omic' technologies has favored the emergence of a new paradigm in biology. By integrating large, complex data sets from different types of sources, systems biology addresses properties of biological systems that cannot be understood through traditional approaches applied in isolation. Utilizing bioinformatics databases and tools, a reversible-action framework enabling the comprehensive reverse construction and analysis of signaling, regulatory, and metabolic systems from experimental high-throughput data are developed. This modeling framework greatly expands the range of biochemical systems open to study with systems biology; it requires only an interaction database and can be supplemented with networks containing only a handful of components. This novel approach is significantly more powerful than previously reported reverse modeling methods. Importantly, even small systems can yield molecular level interpretations of a complex disease, providing insight into disease-modifying pathways that have so far escaped attention. These studies build upon prior evidence from systems biology studies of other human diseases, including Alzheimer's, Parkinson's, and various cancers.

4.2. DATA INTEGRATION TECHNIQUES

Various network propagation algorithms were tested on a large random network to assess the effect of the parameters on the network propagation process. A decision algorithm was also created which can be adjusted to allow for user-defined filtering of content view. This approach also offers a common framework in which network construction, diffusion model selection, and model fitting take place. Kinetic and information-theoretical measures were computed for each node and community in the WT and mutant networks, to provide insight into the fundamental differences between the two. Lateralization cannot be accurately detected by widely used metrics based solely on degree or the clustering coefficient, suggesting that metrics based on the betweenness centrality should be combined or used instead. However, an intrinsic property of networks makes lateralization detection extremely difficult [27]. The treatment of complex chronic inflammatory diseases such as AS and CAD requires multifaceted management approaches targeting drug discovery and treatment optimization. Applying systems approaches, the intersection between AS and CAD was elucidated. Recurrent observations were made regarding protein-protein interaction analysis of candidate genes, the identification of TNF, IL-6, IL-17, and IL-23 as key mediators of inflammatory signals, involvement of NF-kB- and Jak-Stat-mediated signaling in the pathogenesis of both diseases, and underlying genes with distinct neuroregulatory roles that are potential candidates in CAD. Inhibitors of TNF, IL-6, and IL-17 have been widely used in both diseases. Novel drug candidates with therapeutic potential for both diseases were identified.

4.3. MODELING APPROACHES

Systems approach including computational and mathematical approaches has been applied in a number of fields like physics, biology, economics, sociology etc. for the analysis, modeling and understanding of the complexity of systems. The concept of systems biology refers to the interdisciplinary approach that focuses on the structure and dynamics of biological networks. Systems approach including computational and mathematical modeling approaches have been applied in rheumatology for a better understanding of the complex interactions of systemically acting molecules in autoimmune rheumatic diseases. Systems approaches can be always classified into: (1) network-based modeling, and (2) dynamic based modeling. Network-based modeling approaches build networks based on comprehensive information like protein-protein interactions or pathways, and analyze the networks for further understanding of disease. Dynamic-based modeling approaches select a specific biological process based on available experimental observations or computational predictions, and develop differential equations that quantitatively describe the process amenable to heuristic search for models that best fit the observations. There is an increasing interest in sharing of public datasets, and subsequently developing models from the datasets in a systems biology approach of diseases. On the other hand, due to the complexity and ambiguity of the data, an increasing number of studies

have been conducted on robustness and uncertainty of models. Although there are some computational tools or frameworks, the tool-specific biological applications or the top-down applications of the tools have not been developed, yet. Overall, there is a long way to go in bridging systems approaches into the field of rheumatology. In a distinct effort, a systems-level approach to elucidate shared pathways of disease and potential drug targets among AS and CV was provided. For this purpose, integrated multi-omics data was used including protein-protein interaction (PPI) networks, gene expression profiling, and drug-disease relationships. Shared Pathways of Disease is defined as biologically significant pathways that play important roles in multiple diseases. Global view of the disease model that a systematic analysis of both protein-protein interaction (PPI) networks and gene expression profiling indicates that both AS and CVD equally belong to the inflammation pathway in different stages. Quantitative view of drug repositioning and target gene screening and the results indicated that both disease genes and drug targets of Core Inflammation pathway are potentially promising for future studies. This study on a collaborative platform focused on the integration of multi-omics dataset and systematic analysis to identify shared pathways of AS and CVD potentially useful for future drug repositioning. Unlike previous studies on either AS or CVD only, this work systematically investigated the shared pathways of two diseases using multi-omic datasets including PPI networks and gene expression profiles [28].

5. Shared Pathways

Ankylosing spondylitis (AS) is a kind of chronic inflammatory arthritis that mostly affects the spine. It is difficult to diagnose and has a progressive nature that negatively impacts the patient's quality of life by inducing disabilities and causing severe pain. In recently decades, AS has been increasingly recognized to be a systemic disease, which is closely associated with multiple comorbidities including cardiovascular diseases (CVDs), metabolic syndrome, inflammatory bowel disease, osteoporosis, and psychiatric disorders. Among these, CVDs have drawn the attention of researchers as the leading cause of morbidity and mortality in patients with AS. Pathogenic factors of AS such as inflammation, autoimmunity, enthesis, genetic susceptibility, and gut microbiome might also contribute to the elevated risk of cardiovascular events in patients with AS. However, the mechanism underlying the strong predictive correlation between FRS and AS has not been elucidated. To capture hidden, complex relationships between AS and CVDs, analyzed the gene expression profile of AS and CVDs and obtained DEGs associated with both AS and CVDs, which were further subjected to integrated analysis. Pathway enrichment results demonstrated that DEGs shared by AS and CVDs were enriched in pathways such as FA metabolism, TNF signaling pathway, NF-kappa B signaling pathway, Chemokine signaling pathway, Cytokine-cytokine receptor interaction, and Toll-like receptor signaling pathway, which were closely related to inflammation and atherosclerosis. The co-expressed network constructed on the relationships between DEGs and pathway genes can elucidate the potential mechanism underlying the close relationship between AS and CVDs. Individual diseases are usually studied separately. With advancement in systems biology and bioinformatics, researchers have turned to explore shared molecular characteristics/pathways of multiple diseases or drug effects. Nevertheless, studies aiming at revealing shared pathways between AS and CVDs are lacking. To obtain insight into the relationship between AS and CVDs, AS-related differentially expressed genes (DEGs) and CVDs-related DEGs were retrieved. Shared DEGs within two disease cohorts were identified and their enrichment analysis revealed their involvement in inflammation and atherosclerosis-related pathways, indicating the pathogenic similarity between AS and CVDs [22].

5.1. IMMUNE SYSTEM PATHWAYS

The analysis of the immune system pathways shared between AS and CVD identified a few common pathways, including TGF-beta signaling, activation of the IL-6 signaling by the IL-6, TNF-alpha and IFN-gamma cytokine, TNF-alpha signaling via NF-kB, signaling pathway regulating pluripotency of stem cells, and proteoglycans in cancer. Then, the genes discriminating AS among the common gene products in the two disease contexts were extracted along with the corresponding genes accounting for the significant genes in CVD. Prevention and control of AS have secondary significance in the control of CVD in AS population 16. It was indicated that the shared pathways mainly include miRNA-regulated pathways thus disclosing the plausibility of observation in cross pathway regulation. The IL-6 signaling pathway is one of the shared pathways between AS and CVD. However, in-depth discussion of this pathway needs to be differentiated between these two diseases. Its involvement in CVD was further suggested by the ICAM-1-targeting miRNA's regulation in CVD pathway controlling smoking-induced inflammation and atherosclerosis by inhibiting IL-6 and COX-2 expression and associated up-regulation of MCP-1 and ICAM-1 4. Yet, a noted difference is that besides high concentration of IL-6, a low concentration of IL-6 possesses a potent immunoregulatory function on the antigen presentation and pro-inflammatory status of dendritic cells in AS and was shown to promote Th2 and Th17 differentiation. Thus, it is speculated that though elevating IL-6 could promote inflammatory cytokine production and exacerbate AS, aCS does not preclude the existence of the part-like effects of IL-6 thus needs further examination on high mobility group-1 protein relating pathways regulating IL-6 secretion/plasma concentration along with the possible attunement of other genes in AS-CVD context. The TGF-beta signaling pathway is also shared between AS and CVD. It mainly regulates the IL-6 cytokine secreted from both SAA and CD14+ monocytes and can lead to the secretion of IL-6 and TNF-alpha in human atherosclerotic plaques. It also modifies the cellular microenvironment thereby enhancing the genesis of AS in a bone turnover independent way. Mechanobiological studies observed that TGF-beta1 up-regulated Smad7 and down-regulated Smad2. Smad7 also inhibited TGF-beta signaling and the increase of both Smad1 and Sco-2. Thus, the TGF-beta signaling pathway may exist alternative routes for interaction between AS and CVD by either aberration in ligands or cross-organism pathway disruptions [22].

5.2. METABOLIC PATHWAYS

A decrease in glucose levels after a stress test is a common finding during an episode of ankylosing spondylitis (AS) activity. It is hypothesized that an increase in glucose uptake compared with healthy controls is attributable to an increase in the expression of the glucose transporter GLUT4 protein due to circulatory pro-inflammatory cytokines, especially TNF-α. Subsequently, the increase in glucose uptake leads to glucotoxicity. Altered glucose metabolism can lead to inflammation, and inflammatory cytokines can modulate glucose metabolism (13). Further studies are needed to elucidate the mechanisms underlying this relationship and how it promotes the risk of cardiovascular disease among AS patients. Despite its importance, the link between inflammation and atherosclerosis is not well understood and the subject of many studies. Three main metabolic pathways associated with AS-CVD comorbidity were identified: oxidative stress, angiogenesis, and related pro-inflammatory cytokines, especially TNF-α, CRP, IL-1β, IL-6, and IL-8. RAGE, CD36, TLR-2, and TLR-4 could be modules in shared pathways and interact with pathways implicated in both diseases. A greater understanding of the metabolic processes involved in AS-CVD comorbidity may help identify novel therapeutic approaches targeting both disease mechanisms. It would also inform additional studies examining metabolic pathways involved in inflammation and other cardiovascular risk factors in AS, such as hypertension, hyperlipidemia, and hyperglycemia. This study integratively analyzed the crosstalk between AS and CVD using a systems biology approach. A wide range of bioinformatic and mathematical approaches were employed to identify novel comorbidity mechanisms as well as drug-target-disease interaction information [23].

5.3. ENDOTHELIAL DYSFUNCTION

Reports on the risk of cardiovascular and cerebrovascular diseases in individuals with AS, RA, and PsA are scarce. However, AS has been shown to be independently associated with an increased risk of MIs, stroke, and mortality. The authors aimed to provide insight into the risk of these diseases in men and women with AS in a population-based study utilizing the UK Biobank data, and asked how the risks in AS compare with those in RA. In a cohort of 60,222 AS patients matched with 300,902 controls, multivariable Cox regression models were used to estimate hazard ratios (HRs) for MIs and stroke among AS patients relative to age-, sex-, and ethnicity-matched controls, while controlling for other cardiovascular risk factors. Analyses were stratified by sex and adjusted separately for BMI, smoking status, and hypertension. Further Cox regression models were used to assess how AS risk estimates differ from RA patient estimates. AS was associated with a significantly increased risk of MIs (HR=1.42 [95% CI 1.34 to 1.52]) and stroke (HR=1.25 [95% CI 1.19 to 1.31]). Comparative analyses demonstrated significant differences in HR estimates for MIs (HR difference=0.15 [95% CI 0.03 to 0.27]) but not stroke (HR difference=0.020 [95% CI -0.17 to 0.13]). Patterns of associations were relatively consistent across sexes, and risk estimates were markedly attenuated but remained statistically significant after adjusting for individual cardiovascular risk factors, especially hypertension and BMI. This population-based study in a large dataset of individuals with AS versus matched controls provides robust epidemiological evidence that AS is a significant risk factor for MIs and stroke, independently of other cardiovascular risk factors. Comparative analyses further suggest that AS patients are at higher risks of MIs but not stroke when compared with RA patients [17].

6. Clinical Implications

The complex pathways leading to impaired cardiovascular health in ankylosing spondylitis (AS) are only partially elucidated. Cardiovascular abnormalities are frequently encountered in inflammatory rheumatism, with AS associated with an increased burden of atherothrombotic and valvular heart disease. Conventional and traditional cardiovascular risk factors account for only a minority of cases of increased morbidity and premature mortality. The contribution of factors rarely measured in routine practice, including inflammatory, immunological, hormonal, and metabolic factors, is less clear. Even though AS provides a natural experimental model of systemic inflammation, it remains uncertain how immune activation plays out in different tissues and how it translates into a near 50% higher risk of cardiovascular events compared to the general population. In addition to a prioritization analysis discussing the relevance of additional interactions for induced cardiovascular pathologies, the current model supported by existing data provides an interacting systems view of mechanisms whereby the shared impact of disease-related parameters including inflammation, hypoxia, elevated lipid levels, and disturbances of the renin-angiotensin-aldosterone-system contribute to activation of diverse parallel cardiovascular pro-pathologies at induced latencies. A systems biology graph-based analysis approach can assist in understanding how the disease processes in AS, which are complex and multi-parameterial, impact on parallel pathways leading to cardiovascular disease. Shared aspects between AS and cardiovascular disease processes can be defined and prioritized to weigh their relevance for targetable drug effects. Undescribed interactions can be predicted, guiding further experimental design and analyses. Graph visualization is biochemically intuitive and resembles pathways in textbooks, with more complex analyses tedious to interpret. Thus, the analysis of examples may serve to convey the power of the approach to an audience with a broad range of expertise. The large pathways discovered can be viewed as an initial assessment of how disease processes lead to impaired cardiovascular health, applied to the case of AS. It is hoped that the methodology and example analyses may stimulate new avenues of research and discussions between molecular biologists, systems biologists, rheumatologists, cardiologists, bioinformaticians, and researchers in general.

6.1. RISK ASSESSMENT

Cardiovascular (CV) disease is one of the leading causes of morbidity and mortality among the general population. Concomitantly, the existence of chronic inflammatory diseases and CV disorders has been

marked from a historical point of view. In particular, ankylosing spondylitis (AS) is one common form of spondyloarthritis (SpA), and growing evidence suggests that AS can increase the risk of CV disease. While peer-reviewed literature exists with a retrospective and cross-sectional design assessing the relationship between AS and the risk of CV disease, there are limited population-based studies regarding this issue. Based on a bidirectional approach, it is aimed to provide a review of the existing databases regarding various diseases' risk of developing AS. Moreover, patients diagnosed as AS by experienced rheumatologists were checked from the registry-based cohort in South Korea. Data of general population individuals without a prior diagnosis of AS were selected to form a non-AS group. Comorbidities were identified using the codes. Patients in the AS cohort were matched 1:1 with patients in the non-AS cohort based on age, sex, income status, region of residence, and index year. A total of 175,172 patients were finally included in each cohort after applying the abovementioned exclusion criteria. It is globally estimated that there are more than 5 million people with AS, and the social demands for the treatment of this condition will increase over time [20].

6.2. THERAPEUTIC STRATEGIES

Expert recommendations to reduce cardiovascular risk. Therapeutic strategies to reduce the risk of cardiovascular disease in axial spondyloarthritis are based on expert recommendations. Therapy with statins may be considered when the 10-year risk of cardiac or cerebrovascular events exceeds an absolute risk of 20%. Screening of spondyloarthritis patients should be considered following the 2021 European Heart Rhythm Association Guidelines for Spondyloarthritis. Accordingly, it is recommended to exclude coronary artery disease in patients with stable systemic inflammatory disease aged 40 years and older and at least 10 years of disease duration, particularly following the first cardiac manifestation, and in those with increased traditional risk factors. Older age, family history of vascular disease, aortic regurgitation, increased inflammatory parameters, LVH, elevated troponin, and cTnI levels are risk factors for atrial fibrillation in newly diagnosed spondyloarthritis and suggest that further screening should be considered [4].

6.3. PATIENT MANAGEMENT

Cardiovascular disease (CVD) is known to be an important cause of morbidity and mortality in patients with ankylosing spondylitis (AS), which is used interchangeably with axial spondyloarthritis (AxSpA). Since earlier studies revealed that the risk of an atherosclerotic CVD may be increased in AS and other chronic inflammatory diseases, there is an ongoing increasing awareness of CVD risk in these patient populations. Epidemiological studies have clearly demonstrated that AS is associated with increased mortality, mainly due to extra-articular manifestations, including CVD. Patients with AS are also at increased risk for ischemic stroke, and a significant association with stroke can be observed as early as in young patients. Although most studies report an elevated all-cause mortality, the magnitudes of different causes of death in AS remain controversial. While lung disease, and especially pulmonary fibrosis, may be a major cause of death in AS based on population-based cohort studies, other individual studies identified CVD as the leading cause of death. Notably, several variables (such as disease duration, gender, and use of biological DMARDs [bDMARDs]) may influence associations between AS and underlying causes of death. With increasing awareness of CVD as a comorbidity in AS and the advent of new therapies to reduce inflammation and modify the course of diseases, investigation into the risk of atherosclerosis and CVD in AS was renewed. Chronic inflammation and increased systemic pro-inflammatory cytokines may negatively affect the atherogenic process, significantly elevating the risk of cardiovascular events. Imaging studies such as carotid ultrasound or magnetic resonance imaging can detect subclinical disease preceding events. Therefore, the aims of this study were to investigate the prevalence and extent of subclinical atherosclerosis in patients with AS; assess associations between disease-related factors (disease duration, activity, and bDMARD use) with the extent of subclinical atherosclerosis; and control for potential confounding effects of traditional risk factors on more subtle measures of atherosclerosis [21].

7. Future Directions

A possible approach to the reported differences between coronary artery disease in AS and computed tomographic angiography proven coronary artery disease in other inflammatory diseases is that different imaging modalities might detect different processes or non-process effects [9]. Thus, reporting the differences in the atherosclerotic burden might not summarize the differences well in this context. Angiographic reach might be affected by direct bony involvement, inflammatory non-sense secrecy, and associations with other diseases, such as fibromuscular dysplasia, which are thought to have a hereditary tend, all of which differ from Crohn's disease. However, none of this would posit AS as a disease on its own. Imaging outcomes that lack these pathologies corroborated by histology should be investigated, such as fat composition analysis by magnetic resonance imaging. Increasing awareness of the underlying genetic risk factors may treat AS's associations with a wider spectrum of disease better and further dissect the similarities and characteristics. AS shares all known genetic risk factors of the spectrum of haplotype bis-alleles, yet variants affecting IL1R2 are enriched solely in AS [11]. How the rheumatic backbone reacts similarly and uniquely to these variants across diseases is sure to uncover intriguing processes that predate clinical disease and treatments. In the same vein, genetic studies of patients suffering from both ankylosing spondylitis and other inflammatory disorders will aid in the mechanism-disease disentanglement, and clinically confined cohort studies will bring insight into cardiovascular facets across disease types. A link between AS and CVD has been proposed; however, there is a need for further studies investigating biomarkers to more accurately stratify the cardiovascular risk of patients with AS and therefore improve CVD. The condition has been associated with several comorbidities, one of which is CVD-related injuries. Aberrant atherosclerosis was identified as the underlying cause of these cardiovascular diseases. On the arterial side, measures of conduit vessel stiffness and lumen malformations indicate that dysfunction of large

vessels has been explained as the result of a chronic inflammatory air. Insights into the atherothrombotic process have increased and established the importance of endothelial-to-mesenchymal transition as a key process in accelerated atherosclerosis in AS, which has causative inflammatory components [25]

8. Conclusion

Ankylosing spondylitis (AS) is a chronic inflammatory disease characterized by inflammation of the axial skeleton and the sacroiliac joints. It often includes syndromes affecting extra spinal structures, such as the eyes, skin, and aorta. Importantly, it is also associated with accelerated atherosclerosis and enhanced cardiovascular morbidity and mortality compared to the general population. Patients with AS present with more manifestations of cardiovascular diseases and lost more work productivity due to cardiovascular events. It is well-documented that patients with AS are at higher risk of acute coronary syndrome, cerebrovascular disease, peripheral vascular disease, heart failure risk, and chronic arrhythmias. Notably, cardiovascular death in patients with AS is mainly due to ischemic heart diseases, including myocardial infarction, coronary artery disease, and heart attacks. By comparison, most cardiovascular deaths arise from heart failure in the general population. Clinical and preclinical studies have demonstrated that systemic chronic inflammation is associated with accelerated atherosclerosis in patients with AS. Therefore, it is thought that chronic inflammation probably leads to increased non-traditional risk in this population. Some non-traditional risk factors, such as metabolic syndrome, hyperlipidemia, and vascular endothelial growth factor over-expression, are associated with inflammation. Furthermore, endothelial dysfunction, including impaired endothelium-dependent vasodilation and increased circulating endothelial microparticles, plays crucial roles in the initiation and propagation of atherogenesis. Endothelial dysfunction is also a best-determined factor for cardiovascular diseases. However, the mechanisms and mediators of increased non-traditional risk in patients with AS are not fully elucidated. Compared to the enhancement of systemic inflammation, little is known about the development of atherosclerosis in real time and the contributions of acute versus chronic inflammation to the vigilance of accelerated atherosclerosis in patients with AS. Efforts to understand this phenomenon have focused on the endothelium, which has been proposed to represent an initial step in the pathogenesis and maintenance of atherogenesis. The present review discusses the epidemiology, evidence for impaired endothelial function, and data regarding the efficacy of drugs in reducing endothelial dysfunction in patients with AS [26].

HIGHLIGHTS:

1. Patients with AS face a twofold increased risk of CVD, driven by shared inflammatory pathways such as TNF signaling and NF-κB activation [1].
2. Systems biology identifies endothelial dysfunction and immune-metabolic crosstalk as key mechanisms linking AS and CVD [26].
3. Anti-TNF therapy improves microvascular dysfunction in AS, suggesting repurposing opportunities for CVD risk reduction [4].

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