Review

Pathogenesis of rheumatoid arthritis: one year in review 2024

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease characterised by joint destruction and extra-articular manifestations. Different cells and soluble components of the innate as well as adaptive immune system actively contribute to the amplification and perpetuation of the inflammatory processes and structural changes. To date, the knowledge on the mechanisms involved in RA pathogenesis is increasingly precise, mainly due to the recent data obtained from studies on genetics and molecular and cellular biology. In this review article we summarised the new insights into RA pathogenesis from original research articles published in the last year.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease characterised by joint destruction and extra-articular manifestations. The mechanisms underlying RA pathogenesis involve several cellular components of the innate as well as adaptive immune system, leading to the amplification and perpetuation of the inflammatory processes and structural changes (1). Due to recent advances in the research field of RA, some important aspects of the mechanisms involved in the pathogenesis are better characterised and novel pathways of the disease have been identified. Every single element that emerges from basic and clinical research actively contributes to the identification of potential new therapeutic targets, useful for developing a patient tailored therapy. In this review article we summarised the results of a Medline search of original research articles in English published in the PubMed database from January 1 to December 31, 2023.

Genetic and epigenetic advances

Complex interactions among genetic predisposition, epigenetic regulation, and environmental factors lead to the development of RA. To date, outstanding progress has been made in defining the mechanisms underlying RA pathogenesis. However, several aspects of the disease are largely unknown and they remain to be clarified. In the last year, several studies have been conducted in order to evaluate genetic and epigenetic modifications associated with RA, analysing their link with severity degree of the disease, its clinical progression and response to therapies for further developing personalised approaches that can counteract these genetic modifications (2-4). The most investigated and characterised genetic association in RA concerns the HLA antigen, particularly alleles in the HLA-DRB1 locus. However, other non-HLA loci and genes are recognised to be involved in the development and progression of the disease. From the analysis of the expression of quantitative trait loci (eQTL) in naive RA patients, by using sequencing RNA from blood samples and synovial biopsies, 898 eQTL genes were identifies, 232 of which were common between blood and synovium compartments. Particularly, a specific eQTL on HLA-DPB2 with the critical triad of single nucleotide polymorphisms (SNPs) rs3128921, guiding synovial expression of HLA-DP2, was discovered in the HLA region. Its gene expression correlates with increased disease severity and a higher risk of developing a lymphomyeloid phenotype, identifying potential novel therapeutic approaches from the time of diagnosis (5). The most recent studies conducted in the genetic field were primarily focused on the identification and characterisation of new

DNA polymorphisms associated with RA development or rapid progression of the disease, as well as their potential use as biomarkers. In a study conducted in Poland, a significant association emerged between the development of RA and nine genetic polymorphisms related to DNA repair genes. These genetic polymorphisms have been identified as potential triggers for the development of the disease, and their usefulness as biomarkers has been hypothesised. Their presence could indicate a genetic predisposition, leading to increase the risk of developing RA in individuals belonging to this specific population (6). In parallel to the discovery of genetic variants associated with a higher risk to develop RA, special attention was given to genetic variants that can exert protective roles. This is the case of the variants SMAD2 rs1792666 and SMAD7 rs3736242 as well as SMAD4 rs12456284 and rs10502913, all of them belonging to a class of proteins involved in the regulation of transforming growth factor-β (TGF-β) activity, whose presence has been associated to the protective effect against the development of RA (7). Therefore, from the comparison of gene variants between RA and other autoimmune diseases was possible to identify which genetic factors associated with RA predispose to the development of other autoimmune diseases or *vice versa* might exert a protective effect (8). Through genetic analyses in RA patients using in parallel different biological samples (blood, bone marrow, and spleen), STAT3 mutation resulted to be much more frequent in those patients with T-cell large granular lymphocytic leukaemia (T-LGL) than those with Felty's syndrome, highlighting a possible link between this genetic mutation and the development of T-LGL in RA patients (9).

In recent years, particular relevance has been given to genetic studies that focused on analysis of miRNAs as regulators of the immune response. They are non-translated RNA sequences that elicit negative control over protein expression, and their identification and characterisation has made it possible to design novel therapeutic approaches for RA. For example, in the adipose tissue derived from RA patients, an inverse association between IL-6 production and miRNAs expression profile has been demonstrated. The IL-6 mRNA, contributing to the inflammatory state of the disease, exerts a negative effect on the miRNAs expression profile, and tocilizumab, by blocking IL-6 receptor (IL6R), was able to counter IL-6 effects on the miRNAs transcription profile (10). Thus, the results of these recent studies strongly support the usefulness of certain miRNAs as biomarkers of disease activity and allowed to identified novel targets for further pharmacological approaches.

In addition to the innovative studies on the regulation of miRNAs, particular attention has been given to the role of epigenetic modifications, including histone modifications, DNA acetylations, or methylations, in the complex mechanisms underlying RA pathogenesis. By analysing synovial tissues from human knee joints, 6 RNA modification-related genes (ADAMDEC1, IGHM, OGN, TNFRSF11B, SCARA3, and PTN) were discovered, whose methylation influences disease activity in RA as well as osteoarthritis patients (11). Studies on DNA methylation, conducted in the peripheral blood of RA patients and control groups, proved that the levels of CXCR5 methylation, particularly in the cg04537602 promoter region, were significantly higher in RA patients compared to osteoarthritis and healthy subjects, and this also correlated with a higher level of C-reactive protein (CRP), rheumatoid factor (RF) positivity and a high number of involved joints (12). Furthermore, DNA methylation data allowed to improve the identification of potential biomarkers of disease activity, but recently the hypomethylation of the TNF-α gene, which plays an important role in RA, has been recognised to be predictor of disease development. TNF-α gene promoter methylation occurs differently in subjects with RA compared to healthy subjects, allowing early diagnosis in those patients who develop initial inflammatory symptoms even when anti-citrullinated protein antibodies (ACPA) are negative (13). We have to take in account that hypomethylation has been found not only in the TNF-α, but also in the CDKN2A promoter. Thus, excessive hypomethylation of CDKN2A promoter was observed in the peripheral blood mononuclear cells (PBMCs) purified from RA as well as from systemic lupus erythematosus (SLE) patients, leading to hypothesise that CDKN2A methylation levels in PBMCs could be used as diagnostic as well as prognostic biomarkers in RA and in other autoimmune diseases (14). These findings introduce new perspectives in understanding the molecular mechanisms involved in RA pathogenesis and could provide relevant insights for the development of targeted therapies based on the regulation of genetic and/or epigenetic modifications.

Take home messages

- Despite the HLA antigen, including alleles in the HLA-DRB1 locus, other non-HLA loci and genes are involved in the development and progression of RA (2).
- Genetic variants SMAD2 rs1792666, SMAD7 rs3736242 and SMAD4 rs12456284 and rs10502913, associated to high risk of developing RA, can exert protective roles in RA development (7).
- Certain miRNAs were defined in RA as biomarkers of disease activity and made it possible to identify novel targets for further pharmacological approaches (10).

New insights into environmental factors

While the exact cause of the development of RA is not fully understood, genetic susceptibility and exposure to environmental factors are known to exert an active contribution. Smoking, poor diet, obesity, lack of physical activity and psychological stress are able to trigger several pathways involved in the inflammatory processes underlying RA. Up to now, an unhealthy lifestyle has been recognised as one of the causes of increased prevalence of cardiovascular diseases (CVD) in RA patients compared to the general population (15), suggesting the potential role of lifestyle also in the development of co-morbidities. In the recent years, particular at-

tention has been given to define the dietary plan for RA patients and to identify diet intervention for reducing disease activity and to improve their quality of life. Among the different dietary plans actually available, the Mediterranean diet is primarily composed of plant-based foods such as fruits, vegetables, whole grains, seeds, legumes, olive oils, and fish with associated moderate dairy intake and minimal consumption of animal fats. Up to know it is well known that the Mediterranean diet and its specific components are associated with anti-inflammatory effects, leading to improve clinical manifestations and development of co-morbidities in RA patients. In fact, this diet plan might exert both protective and beneficial effects against obesity, development of CVD and metabolic disorders. Several studies demonstrated that in RA patient dietary interventions with plant-based or Mediterranean diet, together with physical exercise programs, contribute to decrease disease activity, improve metabolic status with low-moderate disease activity (16), and exert beneficial effects on glucose metabolism (17). Moreover, weight loss in RA obese patients by dietary intervention promotes enhancement in RAPID3 with increased levels of adiponectin and decreased levels of leptin, with consequent improvement in DAS28 and HAQ-DI (18). In addition to healthy diet and regular exercise, other lifestyle behaviours, including not smoking, moderate alcohol consumption and normal BMI, are associated with a lower risk of developing RA. The underlying metabolic mechanisms has been recently characterised showing that the most pronounced contribution to the positive coefficient of the metabolic signature came from total choline, the percentage of linoleic acid/omega-3 fatty acid and the average diameter of HDL particles. Furthermore, omega-3 fatty acids and DHA echoing fish/seafood intake are associated with lower risk of developing the disease, and these metabolic mediators are able to promote inhibition of the transcription factors NF-κB and PPARs, all involved in the production of pro-inflammatory cytokines (19). We have to take in account that the reduction of BMI in RA patients may also modify the setting of adipokines, preventing adverse long-term outcomes, including fractures and mortality in older adults, as well as radiographic damage progression (20).

Besides different lifestyles, other environmental factors have been linked to RA development. For example, the exposure to volatile organic compounds (VOC), a common environment pollutant, has been recently link to the development of RA through activation of immune cells and amplification of their activities (21). VOC are organic compounds derived from natural, anthropogenic, or mixed sources; they can be inhaled or absorbed through both gastrointestinal system and integumentary system and in RA patients, but not in the general population an increased urinary concentration of 7 different VOC metabolites, including AMCC, CEMA, DHBMA, 3HPMA, MHBMA3, PGA and HMPMA has been observed (21). How VOC contribute to the pathogenesis of RA has been recently investigated. The primary mechanism by which VOC might exert their toxic effects is through induction of oxidative stress that leads to redox-sensitive transcription factors activation, including NF-κB. Interestingly, among the innate immune cells, macrophages are target cells of VOC, on which they induce amplification of their pro-inflammatory activities. In parallel, it is recognised that VOC exposure contributes to the onset and progression of autoimmunity by acting mainly on CD4+ T cells among the cellular components of the adaptive immune system (22).

In addition to pollutants exposure, virus infections are among the major environmental factors recognised to be triggers of RA development. Besides Epstein-Barr virus (EBV), the role of SARS-CoV-2 infection in RA has gained particular attention in recent years (23-25). The interaction between the SARS-CoV-2 and the cellular components of the innate and adaptive immune systems in RA has been objective of several studies *in-vitro* as well *in-vivo*. In the animal model of collagen-induced arthritis (CIA), in which human fibroblasts-like synoviocytes (FLS) were transduced with lentivirus carrying the SARS-CoV-2 spike protein gene, was possible to demonstrate a slightly increase in the incidence and severity of RA by SARS-CoV-2 spike protein with parallel increased levels of CXCL4, anti-phospolipid antibodies, joint erosion and inflammation, supporting the direct contribution of SARS-CoV-2 spike protein in accelerating the development and progression of the disease (26). Up to now, the research on the role of virus infections and RA development was mainly focused on the effects of single virus or its components on the development and exacerbation of the disease. Therefore, it could be relevant to further investigate the consequence of multiple virus infections in different aspects of RA, including their interaction with cellular and soluble components of the innate and adaptive immune system.

Take home messages

- Mediterranean diet in RA patients contributes to decrease the disease activity, improves metabolic status with low-moderate disease activity and exert beneficial effects on glucose metabolism (16, 17).
- Omega-3 fatty acids and DHA echoing fish/seafood intake are associated with lower risk of developing RA (19).
- The exposure to volatile organic compounds (VOC) has been recently linked to the development of RA through activation of immune cells and amplification of their activities (21).

Novelties in the innate immune response

It is well known that cells and cytokines of the innate immune system are largely involved in RA pathogenesis and that their dysregulation compromises synovial homeostasis, leading to the development of synovitis and erosive arthritis. Research performed during the last year focused on neutrophils and their contribution to some mechanisms underlying RA pathogenesis. It is well known that neutrophils are key cells in the innate immune response, but their pro-inflammatory activities and their contribution in bone destruction in RA

has gained particular interest. Thus, their ability to form neutrophil extracellular traps (NETs) has been linked to the amplification of inflammation in the joint of RA patients, contributing to tissue damage and organ disfunction. Recently, an involvement of NETs in osteoclastogenesis through a RANKL-RANK independent way has also been proposed. It seems that NETs are able to induce CD14+ monocytes differentiation in osteoclasts and also indirectly to influence RANKL expression on T cells (27). By using *in-vivo* animal model, the role of NETs and their carbamylated protein cargo (cNETs) were deeply investigated and it was possible to demonstrate that cNETs are able to promote bone destruction and alter osteoclast biology (27). Parallel to neutrophils, it has been recognised that other innate immune cells such as mast cells (MC) actively contribute to the development of the disease. MC are normally present in human synovia and these cells increase in the joints of RA patients, contributing to inflammation and tissue remodelling. MC can exert pro-inflammatory activities with consequent tissue damage, but they are also able to exert protective roles. This has been recently demonstrated in an *in-vivo* system using TNF-transgenic mice. In this animal model it was possible to establish that MC are required for normal lymphatic function and that approaches to inhibit MC activity exacerbates TNF-induced inflammatory-erosive arthritis with decreased lymphatic clearance (28). In the same animal model, using multi-omic spatial and single-cell transcriptomics, was possible to evaluate in the joint-draining lymph node sinuses during RA development altered cells composition of both innate and adaptive immune system, including lymphatic endothelial cells, macrophages, B and T cells. In particular, loss of lymphatic flow through affected joint-draining lymph nodes leads to promote tight interaction between effluxing macrophages and T cells via ALCAM-CD6 co-stimulation, leading to IgG2b class-switching (29). We have to take in account that the inflammatory milieu in the synovia of RA patients is particularly heterogeneous in terms of cells of the innate immune system. By using multi-model single-cell RNA-sequencing and surface protein data coupled with histology of synovial tissues obtained from RA patients was possible to prove that, according to a certain state of the disease, a particular cell-type abundance phenotype (CTAPs) is prevalent. For example, the presence of CTAP-M phenotype with abundance of myeloid cells, M-CSF, TGF-β and fibroblasts driving myeloid cells into MERTK+ HBEGF+ and SPP1+ macrophages, are mainly linked to wound-healing responses (30). Furthermore, this inflammatory phenotype also includes an inflammatory CD74hi-HLAhi fibroblasts cluster linked to low levels of anti-citrullinated peptides antibodies (anti-CCP) and low disease activity (30).

On the contrary, in the CTAP-EFM subtype has been shown a predominant expression of endothelial cells, fibroblasts and macrophages, the letter with a less pro-inflammatory IL-1β profile, while in CTAP-TF are mainly involved T cells and CXCL12+ SFRP1+ fibroblasts, an inflammatory subset of fibroblasts which the precise function is still under investigation (30). Fibroblasts are recognised as one of the main cells involved in the regulation of RA pathogenesis and highly expressed in human synovia. They produce in the synovial tissue extracellular matrix (ECM) components, contribute to the recruitment of T cells into the inflammatory site and promote angiogenesis mainly through NOTCH expression (31). The hypoxic and acidic environment in the synovia of RA patients is able to regulate fibroblast activities, promoting cell migration, IL-6 production and increasing glycolysis (32). Taken together, all the recent findings support the active role of the innate immune cells, including neutrophils, MC and fibroblasts in RA pathogenesis and contribute to better understand the mechanisms underlying RA pathogenesis, offering novel potential therapeutic targets useful in different stages of the disease.

Take home messages

- The ability of neutrophils to form neutrophil extracellular traps (NETs) was linked to the amplification of inflammation in the joint of RA patients, contributing to tissue damage and organ disfunction (27).
- Mast cells (MC) are required for normal lymphatic function and by inhibiting MC activity in TNF-transgenic mice TNF-induced inflammatory-erosive arthritis is amplified with decreased lymphatic clearance (28, 29).
- Multi-model single-cell RNA-sequencing and surface protein data, coupled with histology of synovial tissues, make it possible to characterise specific cellular components in different stages of RA (30).

Novelties in the adaptative immune response

Among cells of the adaptive immune system, regulatory T cells (Treg) play an active role in the immune response during RA pathogenesis and abnormal Treg/Th17 ratio has been detected in different stages of RA (1). In the CIA mouse model treated with natural Treg (nTreg), the knee joints showed marked inflammatory changes, synovial hyperplasia, inflammatory cell infiltration, severe pannus invasion and bone destruction. However, the mice treated with induced Treg (iTreg) showed almost normal synovial membrane, less inflammatory cell infiltration and pannus invasion with no bone destruction (33), suggesting the beneficial regulatory role of iTreg in the inflammatory processes. Furthermore, overexpression of B lymphocyte-induced maturation protein-1 (Blimp-1) was able to promote differentiation in Treg of CD4+ T cells while suppress the differentiation in Th1 and Th17. Thus, this limits the enhanced effect of CD4+ T cells/CD4CM on cell proliferation, invasion, adhesion and inflammation in FLS (34). As far as microRNAs (miRNAs, miR) are concerned, miR-143-3p has been shown to ameliorate arthritis in CIA model, polarising naive CD4+ T cells into Treg cells (35). Furthermore, DNA hypermetilation at the Smad 7 promoter regions may be responsible of loss of smad7 in CD4+ T cells of RA patients, which may contribute to the disease activity by enhancing Th17 over Treg response (36). Furthermore, the possibility to treat CD4+ T follicu-

lar helper (Tfh) cells-overactive RA by modulating STUB1 has been proposed. Targeting STUB1 and restricting the Tfh cells are identified as novel therapeutic strategies to control the activity of the disease.

In the last year, important studies have been performed in order to better define different T cells subtypes. Previous studies demonstrated that a subset of CD3+ T cells are able to co-express the peculiar B cell marker CD20 in various chronic inflammatory diseases. This CD20 expressing T cell subset exerts proinflammatory activities and they are depleted by anti-CD20 therapies such as rituximab. The role of this specific phenotype in RA has been better defined. CD4+ and CD8+ CD20+ T cells were detected in the lymph nodes and joints of CIA mouse model where actively produce high levels of pro-inflammatory cytokines and are less susceptible to regulation by Treg cells. In addition, they are enriched with CXCR5+PD-1+ TFH and CXCR5- PD-1+ TPH cells, subsets of T cells implicated in promoting B cell response and antibody production within inflamed non lymphoid tissue (37). Thus, it has been suggested that this cell subset may exacerbate inflammatory processes by promoting inflammatory B cells response.

In recent years, T-cell activation Rho GTPase-activating protein (TAGAP), a GTPase-activating protein specific for RhoA, has been found to be associated with the pathogenesis of several autoimmune diseases, including RA. The ubiquitously expressed cytoplasmic protein RhoA, a target factor for TAGAP, is a prerequisite for the induction of adaptive T-cell responses. TAGAP interference exerts its beneficial effects by inhibiting the expression of RhoA and NLRP3, limiting the differentiation of Th17 cells with subsequently improvement of RA symptoms. Thus, TAGAP interference is able to reduce foot swelling, bone destruction, synovial inflammation, and cartilage erosion in CIA model, supporting the beneficial effects of TAGAP interference on limiting RA development (38).

T cells are tightly regulated by the environment and these cells are critically dependent on amino acids uptake, the availability of which exerts a powerful influence on their differentiation. Uptake of amino acids is regulated by specialised transporters, such as L-type amino acid transporter 1 (LAT1), also known as SLC7A5. Thus, LAT1, strongly expressed by synovial CD4+ T cells of patients with active RA, correlates with levels of inflammatory parameters, including ESR and CRP, as well as DAS-28 scores (39). Deletion of LAT1 in murine CD4+ T cells was proved to inhibit the development of experimental arthritis and to prevent the differentiation of CD4+ T cells expressing IFN-γ and TNF-α, without affecting Treg. Furthermore, LAT1 deficient CD4+ T cells are able to reduce transcription of genes associated with TCR/CD28 signalling, including Akt1, Akt2, Nfatc2, Nfkb1 and Nfkb2. Recent functional studies revealed a significant impairment of immune synapse formation in LAT1 deficient CD4+ T cells from the inflamed joints, but not from the draining lymph nodes of mice with arthritis (39). Furthermore, knockout mice for the adaptor NTAL (Non-T cell activation linker), a molecule structurally and evolutionarily related to the transmembrane adaptor LAT, developed an autoimmune syndrome characterised by splenomegaly and the presence of antinuclear antibodies. Of interest, it has been shown that NTAL expression is lower in activated CD4+ T cells from RA patients compared to healthy controls (40), supporting the potential role of this molecule in RA pathogenesis and in some clinical aspects of the disease.

In the complex scenario of T cell regulation, we have to take in account that T cells are able to up-regulate glycolysis and Fatty Acid (FA) as well as cholesterol synthesis in order to provide enough energy to meet biosynthetic demands and clonal expansion. Then, they return to oxidative phosphorylation and FA oxidation when the effector functions are no longer required. However, in chronic inflammatory diseases, including RA, T cells maintain a permanent activated profile that is sustained by an aberrant metabolic profile. Recently, it has been demonstrated that the CD8+ T cell gene expression profile of FA metabolism-related genes was significantly different between untreated RA patients and healthy controls (41), and that in CD8+ T cells from RA patients an altered FA metabolism is present, providing novel potential therapeutic targets to control their pro-inflammatory profile. In the last year particular attention has been given to the role of dopamine receptors (DR) expressed on CD4+ T cells in RA. Different subtypes of these receptors are expressed in immune cells and they are associated with the progression or recovery of RA in humans as well as in CIA model. For example, activation of D2-like receptors was able to mitigate symptoms of arthritis in CIA model, by ameliorating Th17/ Treg imbalance. Furthermore, D2R expressed on CD4+ T cells seem to exert a protective role against the imbalance between pro- and anti-inflammatory T cells subsets and the development of arthritis in the CIA model (42).

Parallel to T cells, advances have been made on understanding the role of B cells in RA. It is well known that B lymphocytes play a central role in RA pathogenesis as the precursors of autoantibody secreting plasma cells, as highly potent antigen-presenting cells, and as a source of various pro-inflammatory cytokines. However, the effects of RA environment on B lymphocyte development remain poorly understood. There have been several studies investigating the role of specific classes of B lymphocytes in RA in order to discover novel therapeutic targets for the disease. Attempts have been made to explore and classify B cell subtypes, as in the recent study performed in the SKG mouse model of arthritis (43). In this model a severe reduction in pre-B cells and immature B cells in the bone marrow of mice with active arthritis has been observed, but no effects on mature naïve B cells number. Likewise, analysis of B cell subtypes and B cells activation in RA reveals that seronegative patients had higher percentage of transitional B cells and naïve B cells compared with seropositive patients, regardless of disease activity and DMARDs therapies (44). Furthermore, by investigating B cells response

against antigens undergoing the three main types of post-translational modification (PTM) it has been observed extensive cross-reactivity of PTM-directed B cells against all three PTM antigens, citrulline, homocitrulline, and acetyl-lysine, as well as specific memory B-cell clusters (45).

In addition, anti-malondialdehyde (MDA)/malondialdehyde acetaldehyde (MAA) immunoglobulin G (IgG) gained more attention in RA due to their association with inflammatory processes and disease activities. Anti-MDA positive B cells have been previously identified in RA synovial tissue, lung and bone marrow, and anti-MDA IgG seem to contribute to the activity of the disease by inducing glycolysis pathways in osteoclasts and triggering bone erosion. Furthermore, patients with RA-associated interstitial lung disease have elevated anti-MAA autoantibodies, and MAA-modified protein have been linked to inflammation and fibrosis in airway epithelial cells. Therefore, the identification of MDA/MAA-reactive B cells at mucosal sites in the lung of ACPA+ subjects and in patients with early RA support the role of MAA in breaking of tolerance at mucosal site, reinforcing the concept of mucosal origin for autoimmunity in the disease (46).

Take home messages

- Abnormal Treg/Th17 ratio has been detected in different stages of RA (1).
- CD4+ and CD8+ CD20+ T cells are present in the lymph nodes and joints of CIA mouse model where exert pro-inflammatory activities and are less susceptible to regulation by Treg cells (37).
- Specialised transporters, such as L-type amino acid transporter 1 (LAT1), strongly expressed by synovial CD4+ T cells of patients with active RA, correlates with levels of inflammatory parameters as well as DAS-28 scores (39).

Conclusions

Over the last year, several research studies have been published shedding additional light on the pathogenic mechanisms underlying RA. In particular, studies on genetic, epigenetic and molecular biology allowed us to better characterised new pathways of RA pathogenesis. Particular attention has been given to the role of the environment on the development of RA, highlighting protective as well as pro-inflammatory roles of different environmental factors in the disease. Both innate and adaptive immune system are active players in RA pathogenesis, but their different cellular components are tightly regulated by genes, molecular and cellular components. All the novelties discovered in the last year in the field of RA pathogenesis allow to identify potential new therapeutic targets, useful for developing a patient tailored therapy.

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