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Topic Review

Wnt Signaling Pathway in Rheumatoid Arthritis☆

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic systemic inflammatory joint disease characterized by the formation of a pannus and joint bone destruction. This leads to deformity, discapacity and a diminished quality of life and life expectancy. The Wnt signaling pathway plays an important role in a great number of physiological processes, and recently has been implicated in the regulation of key cells in bone homeostasis. Recent studies suggest that this pathway plays a role in the pathophysiology of RA by the overexpression of inhibitors like the Dickkopf 1 protein (DKK1) that negatively affects the differentiation and activity of osteoblasts. High circulating levels of this protein have been associated with higher rates of radiological progression and greater disease activity in RA. Not much has been published about this subject in patients with RA, so the role of this pathway and DKK1 in RA it is not entirely clear. More studies in this area could improve our understanding about the differences in RA clinical presentation and prognosis, and even more they could provide new possible therapeutic targets for RA.

Vía de señalización Wnt en artritis reumatoide

Palabras clave:
Wnt
DKK1
Osteoprotegerina
Artritis reumatoide

RESUMEN

La artritis reumatoide (AR) es una enfermedad inflamatoria sistémica crónica, caracterizada por la formación de pannus, destrucción articular, deformidad, discapacidad y disminución de la calidad y de la expectativa de vida. La vía de señalización Wnt juega un papel importante en un sinnúmero de procesos fisiológicos. Desde hace algunos años ha sido implicada en la regulación de células fundamentales para la homeostasis del hueso. Estudios recientes sugieren que esta vía juega un rol en la patogénesis de la AR, mediante la sobreexpresión de inhibidores de esta vía como la proteína Dickkopf 1 (DKK1), la cual afecta de manera negativa la diferenciación y la actividad de los osteoblastos. Niveles elevados de esta proteína se han asociado a mayor progresión radiológica y a actividad de

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la enfermedad. Sin embargo, aún no está claro el papel de esta vía y del DKK1 en la AR. Más estudios al respecto podrían ayudarnos a comprender las diferencias en la presentación clínica y en el pronóstico de esta enfermedad. Adicionalmente, podrían sugerir nuevos blancos terapéuticos.

Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease that affects between 0.5 and 2% of the world population. It is more common in women, and although it can occur at any age, its presentation peak is between 50 and 60 years.[1,2] Its etiology depends on the interaction of genetic and environmental factors. 50% of the risk is attributed to genetic factors.[3,4] If appropriate treatment is not received early, the disease progresses, resulting in joint damage, bone erosions and destruction, which is the leading cause of deformity and inability. Patients suffering from this disease have a 50% higher risk of premature death and their life expectancy is reduced between 3 and 10 years when compared with the general population.[5,6]

The evolution of the disease, without adequate treatment, implies the formation of pannus, in which the synovial membrane behaves like a mass of growing tissue composed by macrophages, osteoclasts and fibroblast-like synoviocytes (FLS). In this sense the FLS play an important role, their activation and proliferation contribute to processes of recruitment, retention and activation of inflammatory cells through the production of cytokines, chemokines and adhesion molecules, formation of new vessels through regulators of angiogenesis and destruction of articular cartilage and bone as a result of the production of collagenases and metalloproteases.[7-9]

The loss of bone mass is a common characteristic in RA, being found since the early stages. Periarticular osteopenia can be seen in the bone tissue adjacent to the joint inflammation. Erosions can be observed at the interface between the pannus and the adjacent bone tissue, which progress rapidly, contributing to deformity and morbidity. In addition to this local involvement, there is also systemic bone loss which affects both the appendicular and the axial skeleton, resulting in an increased risk of fracture.[10,11]

Search Strategy

For this topic review were evaluated clinical trials, observational studies, original papers and topic reviews performed in humans and animal models, published in English and Spanish languages, with no limits in the time of publication. A primary search in Pubmed was conducted using the MeSH terms: Wnt Signaling Pathway, rheumatoid arthritis; articles focused in non-rheumatologic topics, mainly about oncology and ocular pathology were discarded. In addition, it was conducted a secondary search of literature with free terms in relation with the topic of interest of the project (Dkk1, Dickkopf).

Role of Osteoclasts

In the last 15 years, the osteoclast has been identified as the cell responsible for focal erosions in RA. In different murine models of RA, osteoclast-deficient mice do not exhibit bone erosions.[12,13]. In addition, both in murine models and in experimental studies in humans it has been evidenced a possible structural benefit with the use of bisphosphonates in RA, by reducing the bone resorption mediated by these cells.[14,15]

The differentiation of the osteoclasts in the normal process of bone remodeling is dependent of the expression of the receptor activator for nuclear transcription factor κB ligand (RANKL) and the signaling through RANK. The binding of the RANKL to the RANK leads to the recruitment of TNF receptor associated factors (TRAF) which, in turn, result in the activation of transcription factors that are important for the differentiation and activation of osteoclasts. All this is counteracted by osteoprotegerin (OPG), a decoy receptor for the RANKL, which prevents its interaction with the RANK. The balance between the RANKL and OPG in the bone microenvironment is precisely the main regulatory mechanism for the differentiation of osteoclasts.[16] By using immunohistochemistry techniques it has been demonstrated the expression of the RANKL in erosion sites in patients with RA, in the pannus-bone interface and in subchondral sites of erosion.[17] Phase II studies with denosumab, a humanized monoclonal antibody against the RANKL, in patients with RA receiving standard therapy, demonstrated lower progression in erosion rates by MRI at 6 months (RAMRIS score) and in the modified Sharp index (plain radiography) at 6 and 12 months. In the same study it could be seen a significant increase in bone mineral density by dual-energy X-ray absorptiometry (DXA), with significant decrease of bone resorption markers and of cortical bone loss measured by digital radiogrammetry[18-20]

Role of Osteoblasts

Osteoblasts play a critical role in the maintenance of bone mass; they are not only responsible for the adequate bone formation, but they also modulate the differentiation and activation of osteoclasts through the production of RANKL and OPG. They are derived from mesenchymal stem cells and express the Runx2 pro-osteogenic transcription factor. These

cells mature from a non-proliferative matrix producing form (expresses alkaline phosphatase and type I collagen) into one capable of matrix mineralization (expresses osteocalcin and osteopontin). Some of these cells are wrapped in the bone matrix becoming osteocytes, their terminal differentiation state. While these cells mature there is a reduction in the production of RANKL, with a concomitant increase in the expression of OPG.[11,21]

Currently there is no doubt about the efficacy of the disease modifying antirheumatic drugs in the suppression of the inflammation, which leads to a reduction or suppression of the joint erosion process. However, the repair of these erosions by formation of new bone is uncommon, although it has been described mainly in patients with low activity or remission of the disease.[22,23]

A study conducted by Dr. Walsh et al.[24] in a murine model of RA, demonstrated that the formation of mineralized bone is compromised in the sites of erosion, finding a predominance of immature osteoblasts. In the same study was evidenced an increased expression of the Wnt signaling pathway (DKK and sFRP), which is essential for the osteoblast differentiation.

The Wnt Signaling Pathway

The Wnt molecules are a family of structurally related soluble glycoproteins which share more than 20 cysteine residues. These molecules or ligands activate numerous signaling pathways through their binding to one of the 10 receptors of the Frizzled (Fz) family known up till now. Their discovery was influenced by research in murine models of cancer and oncogenic retrovirus. Drs. Nusse and Varmus[25] observed the integration of genetic material of oncogenic viruses into the genome of mice which subsequently would develop breast cancer. This gene was called Int1 (integration). Later it was discovered that this gene was the same Wg (Wingless) known in the *Drosophila* fly. After the discovery of other related genes, nomenclature changed, combining Int and Wg, and the Int1 gene became Wnt1.

Currently, the Wnt genes and the components of this signaling pathway are implied in a broad spectrum of biological phenomena, mainly the embryonic development (organogenesis), oncology and other cellular mechanisms associated with different diseases. More recently, the Wnt signaling pathway has been implicated in the regulation of the activation and the function of osteoblasts and osteoclasts.[11,25,26]

Three different Wnt signaling pathways have been described. In general terms, we talk about a canonical pathway (β-catenin dependent) and a non-canonical pathway, among which there are one calcium-dependent and one called planar cell polarity (Dvl-dependent).[26]

The Canonical Pathway

After being secreted by cells, the Wnt molecules bind to the Fz receptor, which forms a complex with the LDL receptor protein (LRP) that acts as a co-receptor. This binding favors a signaling cascade in which several intracellular proteins are involved: Disheveled (Dvl), glycogen synthase kinase 3β (GSK3β), adenomatous polyposis coli (APC) and casein kinase 1 (CK1). At rest, β-catenin is phosphorylated by GSK3β while it forms a complex with APC, axin and CK1 and is marked for proteolysis by ubiquitination. In the active state, the binding of Wnt with the Fz/LRP complex activates the Dvl protein, which in its active state decouples the multiprotein complex inactivating the GSK3β. This favors the accumulation of β-catenin in the cytoplasm and its translocation to the nucleus where it interacts with the lymphoid enhancer factor (LEF) and the T cell factor (TCF) causing transcriptional activation of specific genes.[7,9] (Fig. 1).

The Non-canonical Pathway

In the non-canonical pathway intracellular events occur independently of β-catenin. In the calcium-dependent (Wnt/Ca^{2+}), the signaling through Wnt (mainly Wnt5a) triggers intracellular calcium release and activation of protein kinase C (PKC) and calmodulin kinase II (CamKII). NF-κB is also activated by this pathway, which seems to be involved in the transcriptional activation of genes encoding proinflammatory citokines and chemokines.

Other non-canonical pathway is the planar cell polarity, primarily related to the organizational regulation of the cytoskeleton. In this pathway the activated Dvl promotes the activation of GTPases of the Rac and Rho families. These, in turn, stimulate the activation of kinases such as JNK and ROK, regulating cell growth and differentiation.[9,27]

Regulation of the Canonical Pathway

The canonical Wnt signaling pathway can be regulated in several ways, although the most studied mechanisms are at the extracellular level. One mechanism involves the Dickkopf (DKK) proteins, which bind to the LRP avoiding the formation of the Wnt-Fz-LRP complex. In addition, in the presence of Kremen proteins they form a complex that internalizes the LRP reducing its availability. Sclerostin and other proteins encoded by the SOST gene block this pathway by their binding to LRP. Another known mechanism is through the soluble frizzled related proteins (sFRP), which contain domains that can bind 2 molecules of Wnt avoiding their binding to the receptor complex.

Other possible mechanisms, although less studied, are at the cytosolic level, at the level of any of the components of the GSK3β-axin-APC tertiary complex, or at the level of the nucleus, regarding the availability of the TCF and LEF transcription factors.[26]

Wnt Signaling Pathway in Rheumatoid Arthritis

This signaling pathway has been implicated in inflammatory diseases such as RA, although the exact mechanism has not yet been fully clarified. Using immunohistochemistry it has been possible to evidence greater expression of β-catenin in

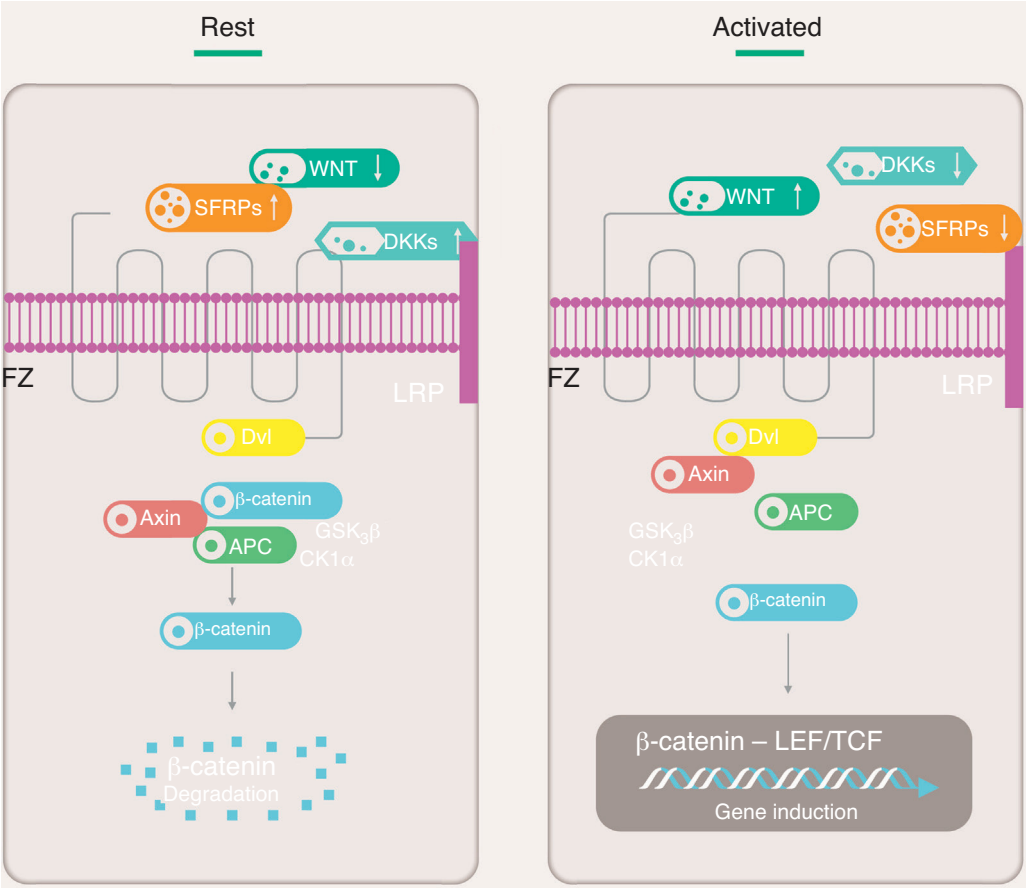

Figure 1 – Canonical Wnt signaling pathway.
APC: adenomatous polyposis coli protein; CK1α: casein kinase 1α; Dkk: Dickkopf; Dvl: Disheveled protein; FZ: Frizzled receptor; GSK3β: glycogen synthase kinase 3β; LEF: lymphoid enhancer factor; LRP: LDL receptor-related protein; SFRPs: secreted frizzled-related proteins; TCF: T cells stimulating factor.

the synovial tissue of patients with RA, when compared with patients with osteoarthritis or recent trauma. In these same samples, using Western blot and RT-CRP, it was confirmed an increased expression of β-catenin in the FLS. In vivo studies have confirmed the expression of Wnt5a in activated blood vessels and FLS in RA, but not in normal tissue. Several research lines suggest that the Wnt5a-mediated signaling plays an important role in the induction of cytokines and other proinflammatory molecules, besides favoring angiogenesis in synovial tissue, positively regulating the vascular-endothelial growth factor (VEGF), and the opposite happens when this pathway is blocked by anti-Fz5 antiserum.[28-30] Moreover, some components of this pathway seem to be affected by epigenetic factors in murine models of RA.[31]

There is enough evidence on the importance of the Wnt signaling pathway in the differentiation, proliferation and survival of osteoblasts, and the inhibition of this pathway, mainly the canonical, negatively affects these cells and therefore, the production of bone both in RA and osteoporosis.[32]

In several studies it has been observed an increased expression of members of the DKK and sFRP (antagonists of Wnt signaling) families in the sites of erosion in animal models of RA. Likewise, high serum levels of Dickkopf 1 (DKK1) protein has been observed in mice models of RA compared with healthy subjects. In this type of murine models it has also been seen that with the use of neutralizing antibodies against DKK1 the destructive pattern characteristic of RA is reversed to one that promotes the formation of osteophytes, like in osteoarthritis, and the inhibition of this pathway through DKK1 in transgenic mice promotes the development of osteopenia.[33,34]

We have already discussed on the multiple and diverse biological processes in which this pathway is involved. In such a complex and multifactorial disease as RA, the Wnt signaling pathway plays different roles in synovial inflammation and bone remodeling. An important characteristic of this disease is the imbalance of the osteoblast-osteoclast axis driven by the joint inflammation. The Wnt signaling pathway plays a critical role in the differentiation of osteoblasts from mesenchymal lineage precursors, and DKK1, a natural inhibitor of this pathway, is important in this regard, affecting this differentiation and the deregulation of osteoclasts in RA. This alteration is not completely covered by current treatments for RA, which are addressed, mainly, to synovial inflammation,

making that molecules such as DKK1 might be in the future therapeutic targets in this disease and thus, along with the anti-inflammatory therapy, they might prevent or correct the bone damage.[35]

However, much evidence confirms that the Wnt signaling pathway is active during the development of the RA, favoring synovial proliferation, synovitis and pannus formation. For example, the activation of this pathway contributes to the formation of osteophytes and to the anabolic model of bone remodeling that can be seen in patients with ankylosing spondylitis, while its inhibition promotes bone erosions and a catabolic model in patients with RA. On the contrary, in FLS and chondrocytes the activation of the Wnt pathway promotes the destruction of the cartilage matrix, the proliferation of synovial tissue and the recruitment of inflammatory cells.[9,36-38]

DKK1 in Rheumatoid Arthritis

DKK1 is an important regulator of bone mass. Its higher expression is associated with osteopenia or osteoporosis,[39] and its reduction, with more bone mass; in fact, studies with antibodies directed against this molecule for diseases such as osteoporosis are currently being conducted.[40]

In a subgroup of patients (113 of 632) randomly chosen, who had previously participated in a study of early RA which compared the efficacy of etanercept vs. methotrexate,[41] measurements of DKK1 were performed by ELISA and it was sought the association with greater radiological progression taking into account the modified Sharp score. In all patients, each increase in one standard deviation in the levels of DKK1 was associated with a RR of 1.65 of progression of bone erosions (CI 95%: 1.06-2.54), and in the same way, when the groups were separated by tertiles, the RR in the higher tertile was 4.6 (1.46-13.8) compared with the two lower. No association was found between the levels of DKK1 and the reduction of the joint space, which is in accordance with the described role of this factor in the regulation of bone remodeling.[42]

In a study conducted in Chinese population in which were taken samples of 300 patients with RA, 150 in whom the duration of the disease was less than one year and 150 in whom it was longer than 5 years, seeking to compare the expression of both DKK1 and OPG (measured by ELISA) at different stages of the disease and to analyze their association with different clinical profiles according to age, gender, acute phase reactants and clinical measurements. In addition, X-rays of the hands of patients with RA were taken and evaluated by radiology experts using the Sharp-van der Heijde method. Patients receiving anti-TNF treatment were excluded. It was found that DKK1 levels were elevated in patients with late disease when comparing them with those with early disease and healthy population (5.87 ± 3.03 ng/ml vs. 1.67 ± 1.15). On the other hand, when compared with healthy controls, the OPG levels were increased in early stages, finding no significant difference when compared with more advanced stages.[43]

In another study conducted by the same group 100 patients with RA were included, 40 of them treated with infliximab and 30 with anakinra, and the same treatment was maintained for 6 months. 140 individuals were taken as control group: 30 with osteoarthritis, 30 with ankylosing spondylitis, 30 with systemic lupus erythematosus, 10 with systemic sclerosis and 40 healthy controls. Measurements of DKK1 and OPG by ELISA, ESR, CRP, anti-CCP and rheumatoid factor were performed, as well as radiographs of hands and wrists evaluated by the Sharp method. The concentrations of DKK1 were significantly higher in the patients with RA compared with the other groups. There also was found an association between the increased levels of DKK1 and the presence of bone erosions, joint space narrowing and Sharp score. Likewise, it was found a correlation between DKK1 and the levels of CRP and ESR. After 6 months of treatment it was found that the DKK1 levels decreased in the subgroup of patients who received infliximab and anakinra. In the case of infliximab this was true in the patients who were catalogued as treatment responders (30 of 40 patients): 6,653.1 ± 3,336 pg/ml vs. 3,424.6 ± 1,918 pg/ml, with a significant p.[44]

A recent study in which patients with RA were taken from the EURIDISS study, which initially included 238 patients with RA of less than 4 years of duration, and were longitudinally followed-up and evaluated after 1, 2, 5 and 10 years, seeking the association between DKK1 and periarticular bone loss measured by digital radiogrammetry with X rays (DXR). A total of 136 patients had radiographs available for a 5 year follow-up and blood samples from the beginning. It was found that the baseline plasma levels of DKK1 were significantly higher in the patients who developed periarticular osteopenia within one year (2,010 pg/ml vs. 1,332 pg/ml; p = 0.03). This difference was not observed in the follow-up at 2 and 5 years.[45] Remarkably, a study conducted in the same group of patients found no association between baseline levels of DKK1 and the radiological progression measured by SHS.[46]

Dr. De Rooy[47] published recently an article evaluating the genetic component of this molecule; the study assessed genetic variants in different proteins involved in the Wnt signaling pathway in relation to the progression of joint damage measured by the SHS method. The study included more than 1,000 patients of 4 European cohorts, including Leiden's. After adjustments and corrections, only 3 variants of a single nucleotide (SNP) for DKK1 maintained statistical significance and, of them, the one that was most associated with joint damage (rs1896368) was also associated with higher serum levels of DKK1 in relation to the other genotypes. Providing further evidence that the Wnt signaling pathway (especially the canonical) and the DKK1, in particular, plays an important role in the mediation of joint damage in RA.[48]

Conclusion

The Wnt signaling pathway plays a very important role in the regulation of bone remodeling, and several of its components are involved in the pathogenesis of different diseases in which the bone is a target organ. In the case of osteoporosis, for example, is being studied a monoclonal antibody against sclerostin (one of the inhibitors of this pathway) which in phase II clinical trials has demonstrated effectiveness quickly

improving the bone mineral density and decreasing the bone resorption markers.[49,50] Efforts have been made to create DKK1 neutralizing antibodies for therapeutic purposes, although there has not been much progress.[32]

There are few studies, from the clinical point of view, about the role of this pathway in RA. However, it seems consistent the association between the DKK1 levels and a greater progression of the bone damage, even in systemic lupus erythematosus, in which this type of commitment is unusual.[51] Some studies suggest an association between the DKK1 levels with the disease activity and acute phase reactants,[43,44] although more studies are required before being able to affirm its usefulness as a biomarker. Future research will help to broaden the knowledge about this pathway and the involved molecules, being able to suggest new biomarkers and therapeutic targets in RA.

Conflict of Interest

The authors declare that they have no conflict of interest.

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