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# A fresh look at angiogenesis in juvenile idiopathic arthritis

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***Abstract***

*Angiogenesis is the complex process of creating new capillaries from preexisting blood vessels due to hypoxemia, injury or inflammation of the tissues. Numerous cytokines and cell mediators have been identified to induce and stimulate angiogenesis, but vascular endothelial growth factor (VEGF) is a key regulator. The role of proangiogenic factors in the pathogenesis of chronic arthritis is currently a subject of intensive investigations in adult patients with rheumatoid arthritis (RA) and, to a limited extent, in children with juvenile idiopathic arthritis (JIA). Recent studies has shown a significant correlation between proangiogenic marker concentrations and the severity of inflammation in either RA or JIA patients. The serum neovascularization markers correlate with the power Doppler ultrasound image of the inflamed joint and hypertrophic synovium, which may be connected with the disease activity.*

*The aim of this paper is to describe the state of the art on the important role of angiogenesis in adult and childhood rheumatoid arthritis.*

***Key words:*** *angiogenesis, juvenile idiopathic arthritis, rheumatoid arthritis, ultrasound.*

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## Introduction

Angiogenesis is the complex process of creating new capillaries from preexisting blood vessels due to hypoxemia, injury or inflammation of the tissues. In normal tissues, angiogenesis is a self-controlled and self-limiting process and is essential for proper functioning of the body. In pathologically altered tissues, the balance between the activity of pro- and anti-angiogenic factors is impaired [1-4].

The proangiogenic mechanism is diverse – the cells stimulate proliferation and maturation of endothelial cells, degrade the extracellular matrix or affect the maturation of blood vessels [5, 6]. The role of angiogenesis in the neoplastic process is the most prominent, but its effect is also observed in non-cancerous diseases such as asthma, psoriasis, obesity, diabetic retinopathy and rheumatoid arthritis (RA) [7].

Juvenile idiopathic arthritis (JIA) is a heterogeneous group of arthritis of unknown etiology that begins before the age of 16 and lasts continuously for a period of six weeks. It is the most common inflammatory disease of the connective tissue in developmental age. It leads to progressive and sometimes permanent and irreversible damage to the musculoskeletal system [8-11].

The pathogenesis of JIA is multifactorial. Various disorders – environmental, genetic and complex immune system – are involved in the development of the disease [12-17]. Although the exact cause of this disease is still unknown, the role of various pro-inflammatory cytokines including tumor necrosis α (TNF-α), interleukin 1 (IL-1) and interleukin 6 (IL-6) is confirmed [18, 19].

Therefore, it is very important to establish a quick and accurate diagnosis. The course of the illness leads to many immunological disorders, including autoantibody production and cytokine imbalance. Infectious agents may further modify the immune response. Correct treatment inhibits the development of the disease [20].

Results of the recent studies showed a significant correlation between levels of proangiogenic factors and JIA activity. In this review we discuss the role of angiogenesis in JIA patients.

## Angiogenesis markers

Numerous cytokines and cell mediators have been identified to stimulate the angiogenesis process (Fig. 1). The proangiogenic mechanism is variable – the cells stimulate proliferation and maturation of endothelial cells (fibroblast growth factor, vascular endothelial growth factor – VEGF, insulin-like growth factor-1), degrade extracellular matrix (metalloproteinases, IL-8) or affect the maturation of blood vessels (platelet-derived growth factor).

Vascular endothelial growth factor is a key regulator of angiogenesis. The VEGF family consists of VEGF-A (commonly referred to as VEGF), VEGF-B,

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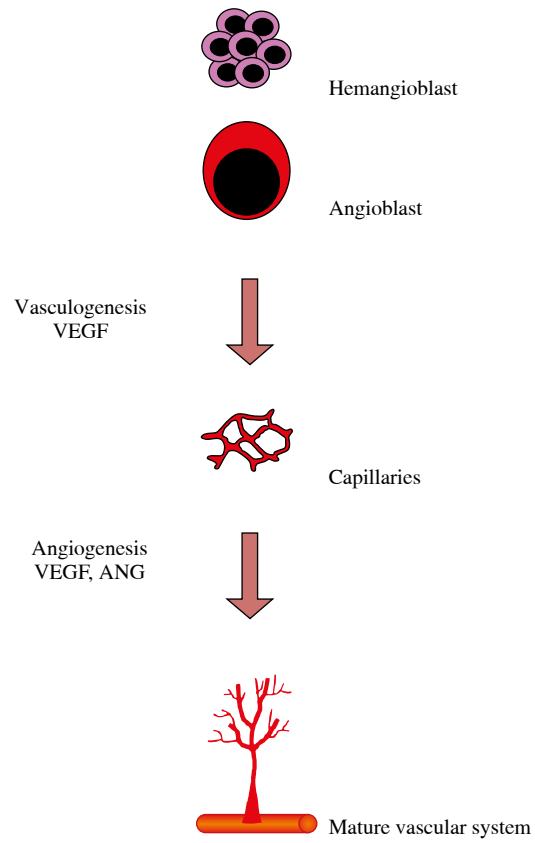


**Fig. 1.** Developmental angiogenesis

VEGF-C, VEGF-D, VEGF-E, VEGF-F and placental growth factor (PlGF). These molecules act on cells by binding to appropriate receptors: VEGFR-1 (Fms-like tyrosine kinase-1 – Flt-1) and VEGFR-2 (kinase domain region – KDR) located on vascular endothelial cells and VEGFR-3 (Fms-like tyrosine kinase-4 – Flt-4), present on lymphoid endothelial cells [21, 22]. Interactions between VEGF family members and their receptors are complex and, depending on the type of connection, initiate appropriate angiogenetic pathways.

Both types of receptors are involved in angiogenesis and vasculogenesis. Although VEGF shows a higher affinity for VEGF-R1, phosphorylation of tyrosine kinase is more potent after binding to VEGFR-2, making this receptor the main receptor for VEGF activity [23, 24]. It appears that the role of VEGFR-1 is to modulate VEGFR-2 activity, acting both proangiogenically and as a "trap receptor".

The last stage of angiogenesis is maturation and stabilization of the vessel, where the angiopoietins are the involved cells. The proangiogenic effect of angiopoietin-1 (Ang-1) is to stimulate the migration of endothelial cells and activate the interaction between them and the underlying membrane. In addition, Ang-1 inhibits endothelial cell apoptosis [25].

Angiopoietin-2 (Ang-2) is mainly expressed in vascular remodeling sites where it is able to block Ang-1 stabilizing action. The effect of Ang-2 seems to be dependent on VEGF. Angiopoietin-2, in the absence of VEGF, causes vascular regression by induction of endothelial cell apoptosis, but in the presence of high concentrations of VEGF it activates the angiogenesis process [26-28].

## Role of angiogenesis in rheumatoid processes

In the pathogenesis of rheumatoid processes, inflammatory cytokines play an important role. In the joints affected by inflammation, they maintain the inflammatory process, but also have a significant effect on angiogenesis. It leads to proliferation of synovium and pannus formation, in which numerous new blood vessels are present [29, 30].

In studies of RA patients, altered concentrations of major angiogenic factors have been demonstrated not only in synovial fluid and synovial tissues, but also in serum [31]. As a result of hypoxia, a hypoxia-induced factor (HIF-1α) is released and stimulates the expression of further proangiogenic factors (Fig. 2) [32, 33]. Vascular endothelial growth factor is the best known angiogenesis stimulating factor and its serum concentration correlates with the clinical picture of RA, as well as C-reactive protein (CRP) level and radiological changes in hands and feet [34]. A similar relationship has been observed in patients with JIA, but only single publications are available in the literature [35].

In addition to VEGF, proangiogenic effects in rheumatoid processes have been demonstrated for a number of other factors, including TNF-α, IL-1, IL-6, IL-8, IL-13, IL-15, and IL-18.

Interleukin 18 stimulates the induction of angiogenesis by VEGF production and affects the endothelial cells through integrin αvβ3. Moreover, it stimulates production of chemokines SDF-1/CXCL12 and MCP-1/CCL2 – complexes that promote angiogenesis in the synovial lining of the joints [36].

Tumor necrosis factor α has a direct effect on angiogenesis. It may also regulate angiogenesis by stabilizing the new vessels through Ang-1 and the Tie-2 synovial membrane receptor [37, 38].

Angiostatin and endostatin, physiologically, act antiangiogenically by reducing VEGF concentrations. Through their influence on integrins, they interfere with the signaling necessary for the development of angiogenesis. Thrombospondin-1 (TSP-1) produced by the synovium of RA patients acts angiostatically inhibiting neovascularization and inflammation of the synovial membrane. Increased intraarticular angiogenesis is also a consequence of insufficient inhibiting effects [39, 40].

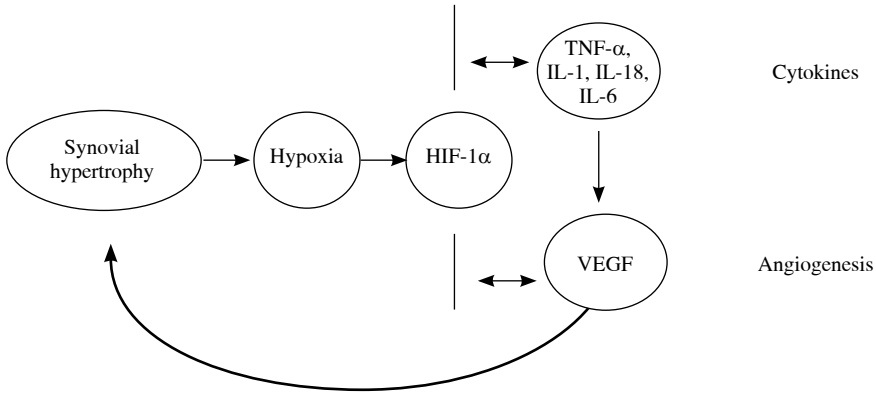


**Fig. 2.** The role of hypoxia in the development of angiogenesis in rheumatoid processes

Anti-angiogenic therapy is currently a new and important goal in the treatment of RA. There are many drugs that inhibit intracellular vascular formation, such as anti-VEGF antibodies (bevacizumab, vatalanib) or JAK inhibitors, but they are still under clinical trials [41].

Ultrasound examination and power Doppler mode is the gold standard in JIA diagnostics. The degree of synovial hypertrophy may be visualized, as well as the blood free movement in vessels of the synovium. It allows one to assess the activity of the inflammatory process, but also may detect subclinical and mild lesions (Fig. 3).

The inflammatory activity of the synovium detected by power Doppler imaging is correlated with inflammatory expression (erythrocyte sedimentation rate – ESR, CRP) and angiogenesis markers, primarily with VEGF. Moreover, in patients with clinical remission, persistent inflammatory activity of the synovium may be visualized, and helps in further therapeutic decisions, but it is not an early predictor of exacerbations [42-48].

## The current state of knowledge on the role of angiogenesis in juvenile idiopathic arthritis

Despite a number of studies on angiogenesis and anti-angiogenic therapy as a novel trend in RA, there have been few publications on the assessment of angiogenic factors in JIA so far.

High levels of VEGF and its soluble receptors have been reported several times in adult patients with RA [48-52]. In studies of Maeno *et al.* levels of VEGF and its soluble receptors (sVEGFR-1, sVEGFR-2) in the serum of JIA patients were significantly higher compared to the healthy group [53]. Similar correlations were observed in our own studies [54]. There have been single reports concerning the VEGF concentration in the synovial fluid in children. In the research of Vignola *et al.* it was found that its concentration in the articular fluid was significantly higher than in the serum concentration in JIA patients [35]. In our own studies, we observed a similar relationship between VEGF and its soluble sVEGFR-1 receptor. The inverse relationship was related to the sVEGFR-2 receptor, which could be associated with high affinity of VEGF to the Flt-1 receptor [54]. In patients with RA – contrary to the results of our research – Lee *et al.* found no significant difference between serum VEGF and synovial fluid taken from 32 patients [55]. Studies of Shahrara *et al.* on the expression of Ang-1 and Ang-2 in the synovium of RA patients revealed its significant increase. In this work the authors also observed high expression of the receptors Tie-1 and Tie-2 in the inflamed synovium [56]. In our own studies, Ang-1 and Ang-2 concentrations were higher in the serum of patients with JIA compared to the healthy controls. In contrast to VEGF, the concentration of both angiopoietins in the synovial fluid of JIA patients was significantly lower than in serum [54]. In the work of Kurosaka *et al.*, the role of Ang-1 was emphasized as an index of persistent arthri-

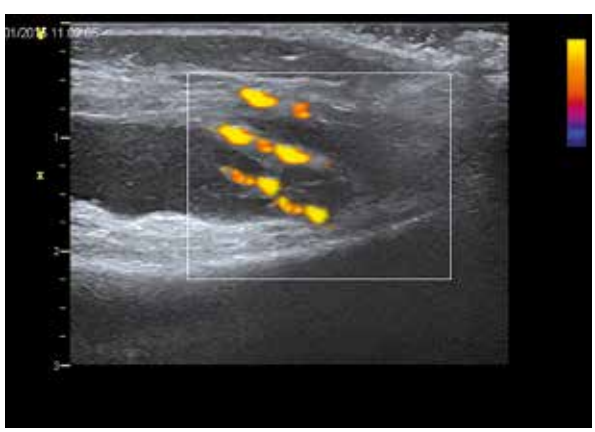

**Fig. 3.** Example of an ultrasound image of angiogenesis in an inflamed joint

tis, while the increase of Ang-2 was observed only with significantly enhanced angiogenesis [57].

Maeno *et al.* studies showed a positive correlation between VEGF and inflammatory markers, such as CRP and ESR [53] in a population of children with oligo- and polyarthritis. Similar observations were made by Sone *et al.* and Lee *et al.* in patients with RA [56, 58]. However, they did not evaluate the relationship between VEGF concentration in synovial fluid and inflammatory parameters.

Ultrasonography in rheumatology is currently a very useful tool in assessment of joint inflammation. In addition to the presence of characteristic lesions, such as synovial hypertrophy or effusion, it is possible to assess slow blood flow in the newly created vessels of the inflamed synovium by the power Doppler technique. The presence of vessels with intense flow indicates the high activity of the disease process, but also allows one to visualize the final stage of synovial angiogenesis [59-69].

Spârchez *et al.* attempted to correlate disease activity with the ultrasound image, confirming that high activity of inflammation is connected with a high degree of vascularization [70]. Moreover, Shanmugavel *et al.* and Magni-Manzoni *et al.* have shown that, even in clinically inactive disease, inflammatory changes in the hypertrophied synovium still remain active. This indicates the need to maintain therapy for patients in remission [61, 71]. Magni-Manzoni *et al*., in a subsequent study, found that subclinical changes of joints detected in power Doppler ultrasonography are not a predictor of disease exacerbations [72].

Despite the large potential for angiogenesis assessment by power Doppler ultrasonography (PDUS) in JIA patients, there has been no work combining PDUS imaging and proangiogenic factors so far.

In studies of patients with RA, both Strunk *et al.* and Gok *et al.* did not detect any significant correlation between the concentration of VEGF and synovial neovascularization evaluated using PDUS [73, 74]. In the same work, Gok *et al.* found a positive correlation between Ang-1 and synovial effusion, but found no such relationship with the degree of synovial vascularization. Similarly, in our own study, a significant relationship between the concentration of Ang-1 and synovial vascularization was not confirmed. Conversely, Ang-2 concentration in patients with JIA was clearly correlated with a high degree of vascularization [54].

Spârchez *et al.* found that a high concentration of C-reactive protein is associated with a high degree of vascularization. In our own studies we observed the same pattern [70].

The role of angiogenesis appears to be crucial in the pathogenesis of JIA. It might be proved by high levels of angiogenic factors and their correlation with disease activity. Vascular endothelial growth factor, the most specific marker of angiogenesis, reflects this correlation. Its concentration in connection with the ultrasound image of the synovium and the degree of vascularization provides information about disease activity in the early stages.

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*The authors declare no conflict of interest.*

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