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Review

Vimentin as antigenic target in autoimmunity: A comprehensive review

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ABSTRACT

Vimentin is a protein of intermediate filament family, which is expressed in all mesenchymal cells. Vimentin plays a key role in the physiology of the cell, cellular interactions and the functioning of the immune system. Post-translationally modified and native forms of vimentin are involved in the pathogenesis of inflammation and many autoimmune diseases: rheumatoid arthritis, sarcoidosis, systemic lupus erythematosus, antiphospholipid syndrome, Crohn's disease, ankylosing spondyloarthritis and idiopathic pulmonary fibrosis. Modifications of the protein lead to the formation of antigenic epitopes and, as a result, to the synthesis of antibodies. Citrullinated, carbamylated and acetylated forms of vimentin participate in the pathogenesis of RA, and antibodies against them serve as diagnostic and prognostic markers of the disease. Epitopes of native vimentin are antigenic in the group of HLA-DRB1*0301 positive patients with sarcoidosis. In addition, vimentin takes part in pathogenesis of tubulointerstitial inflammation and glomerulonephritis in lupus. In antiphospholipid syndrome interactions of vimentin and cardiolipin on the surface of apoptotic cells lead to the formation of an immunogenic complex. Antibodies against vimentin/cardiolipin complex are involved in the mechanism of thrombogenesis and serve to identify patients seronegative for antibodies to cardiolipin and ß2glycoprotein-I with the clinical features. Post-translationally modified form of the protein is citrullinated and MMP-degraded vimentin, which was found in serum of patients with Crohn's disease and ankylosing spondyloarthritis.

1. Structure and function of vimentin

Vimentin belongs to the family of intermediate filaments of cellular cytoskeleton located in cells of mesenchymal origin. Consistent with their diameter, intermediate filaments (approx. 10 nm) are categorized between microtubules and actin microfilaments. Intermediate filaments are important for cellular architectonics because they maintain a spatial distribution of organelles and nucleus inside the cell [1]. Keratin of epithelial tissues, desmin in striated muscle and neurofilaments in neurons represent other types of intermediate filaments [2].

Vimentin is protein with a molecular mass of 57 kDa that is encoded by VIM gene located at chromosome 10p13. It can be found almost in every connective tissue cell including fibroblasts, osteoblasts, endotheliocytes, myoblasts, bone marrow and lymphatic cells, tissue macrophages and thrombocytes [3]. It possesses significant homology across species from cartilaginous fishes (*Scyliorhinusstellaris*), Amphibia (*Xenopuslaevis*) to mammals (*Homo sapiens*) [4].

The tertiary structure of vimentin consists of a central rod of alpha-

Abbreviations: TNF, tumor necrosis factor; IL, interleukin; NK, natural killer; ADP, adenosine diphosphate; SUMO, small ubiquitin-like modifier; PAD, peptidyl-arginine deiminase; RA, rheumatoid arthritis; HLA, human leukocyte antigen; ACPA, anti-citrullinated peptide antibodies; MCV, modified citrullinated vimentin; NET, neutrophilic extracellular traps; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PTMV, post-translational modified vimentin; anti-MCV, anti-mutated citrullinated vimentin antibodies; anti-CCP, anti-cyclic citryllinated peptide antibodies; SLE, systemic lupus erythematosus; TCR, T-cell receptor; 1D-SDS-PAGE, one-dimensional SDS(sodium dodecyl sulfate)-polyacrylamide gel electrophoresis; 2D-DIGE, two-dimensional differential gel electrophoresis; PBMCs, peripheral blood mononuclear cells; ACE, angiotensin-converting enzyme; aCL, antibodies to cardiolipin; aß2GPI, antibodies to ß2glycoprotein-I; APS, antiphospholipid syndrome; aaVC, antibodies against the vimentin/cardiolipin complex; CD, Crohn's disease; UC, ulcerative colitis; MMP, metalloproteinases; TGF, transforming growth factor

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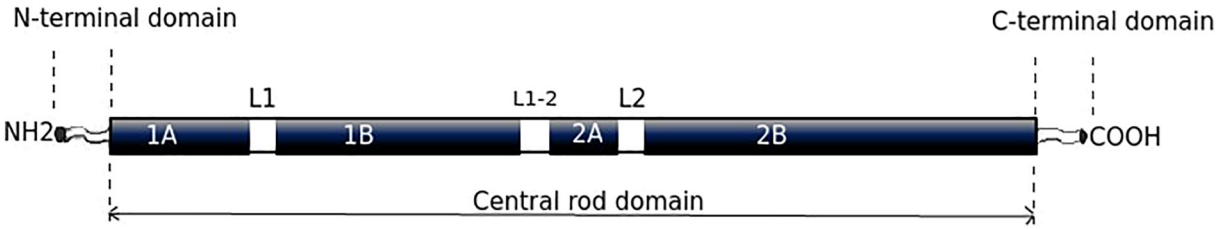

Fig. 1. Structure of vimentin. Vimentin monomer consists of three domains: a central alpha-helix rod, N-terminal (or head) and C-terminal (or tail) regions. The central rod domain consists of four segments 1A, 1B, 2A, 2B, which are separated by L1, L1-2, L2 regions heptad repeats.

spiral that is flanked by N- and C-terminal domain [5]. The central alpha-spiral part of the vimentin molecule is common structure in all intermediate filaments. There are four spiral fragments 1A, 1B, 2A and 2B that are linked with L1, L1–2 and L2 regions of heptapeptide repeats [6] (Fig. 1).

The vimentin alpha spirals are dimerized and antiparallel binding of dimers results in tetramers that are the units for long filamentous structures of the cytoskeleton [7,8]. Vimentin filament is stabilized by several associated proteins like kinezin, dinein and dynactin [6, 7].

Besides compartmentalization of intracellular space, vimentin is involved in several other functions, vividly illustrated by experimental models. In vimentin knock-out mice there are some impairments of wound healing because of defects in fibroblast migration and decrease in homing of lymphocytes due to their adhesion failure [9]. Integrin functions are damaged and trans-endothelial migration of lymphocytes is deteriorated [10].

The vimentin is localized not only in the cell cytoplasm but also in the nucleus and on the cellular surface [11]. The precise mechanisms, which induce extracellular secretion of vimentin filaments are not known, but Mor-Vaknin et al. [12] supposed that the endoplasmic reticulum and the Golgi complex produce secretory vesicles for protein exocytosis. The mechanism was shown for activated macrophages that have expressed phosphorylated vimentin on its surface. Vimentin exocytosis is regulated by cytokines: TNFa induces and IL-10 down-regulates surface expression of the protein (Fig. 2). Another presumed mechanism of vimentin exposition in extracellular space is apoptosis of neutrophilic granulocytes [13].

Further degradation of vimentin protein and its modification during neutrophilic inflammation can be related to the induction of specific autoantibodies in several autoimmune diseases. Extracellular secretion of vimentin was described for several other cell types like platelets, endothelial cells and T-cells [13–15]. Vimentin can be expressed on cellular surface during intracellular infection of macrophage with Mycobacterium tuberculosis and is the ligand for NKp46 receptors of NK-cells [16,17]. Recognition of macrophages that contain mycobacteria by NK cell leads to cell-mediated cytotoxicity and killing of infected cells.

2. Post-translation modification of vimentin

Vimentin undergoes various post-translational modifications such as phosphorylation, SUMO-ylation, ubiquitination, glycosylation, ADP-ribosylation, citrullination and carbamylation [18].

It has been shown that phosphorylation determines the conformation of vimentin and intermediate filament assembly. The main role of phosphorylation of intermediate filaments is to facilitate its

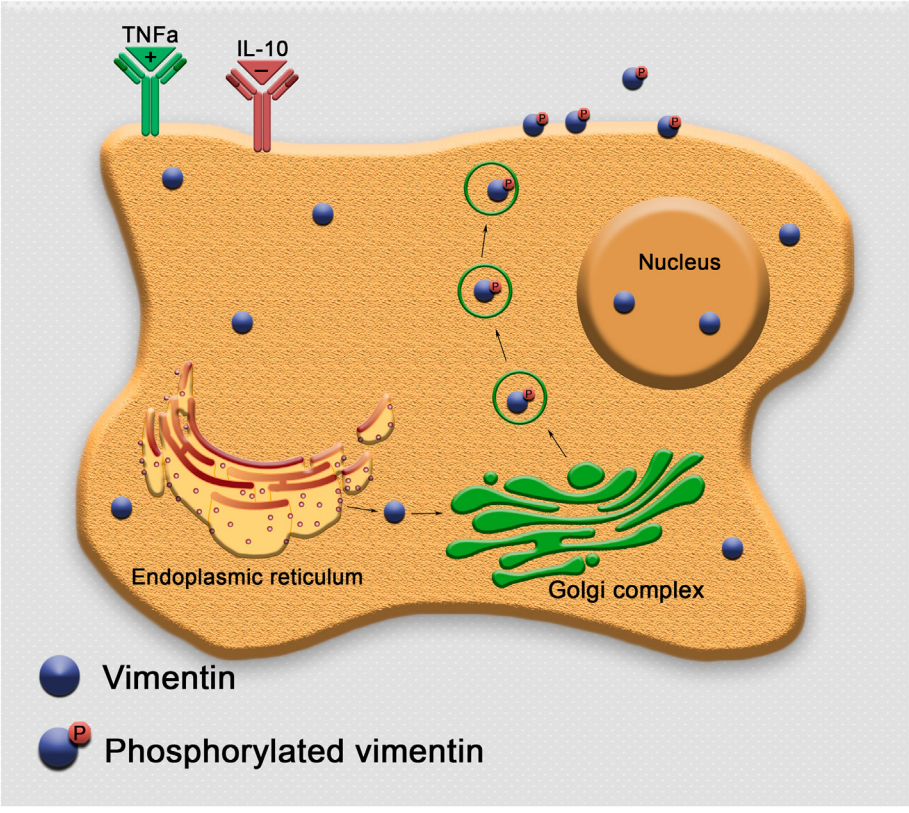

Fig. 2. Scheme of vimentin distribution in the cell. Vimentin can be localized in the cytoplasm, in the nucleus and on the cell surface. Post-translational modified vimentin, such as phosphorylated vimentin, also can be presented on the cell surface. The endoplasmic reticulum and the Golgi complex form vesicles, that are involved in the extracellular secretion of a phosphorylated vimentin. Cytokines can regulate expression of phosphorylated vimentin on the cell surface. TNFa and IL-10 induce and down-regulate exocytosis of the protein respectively.

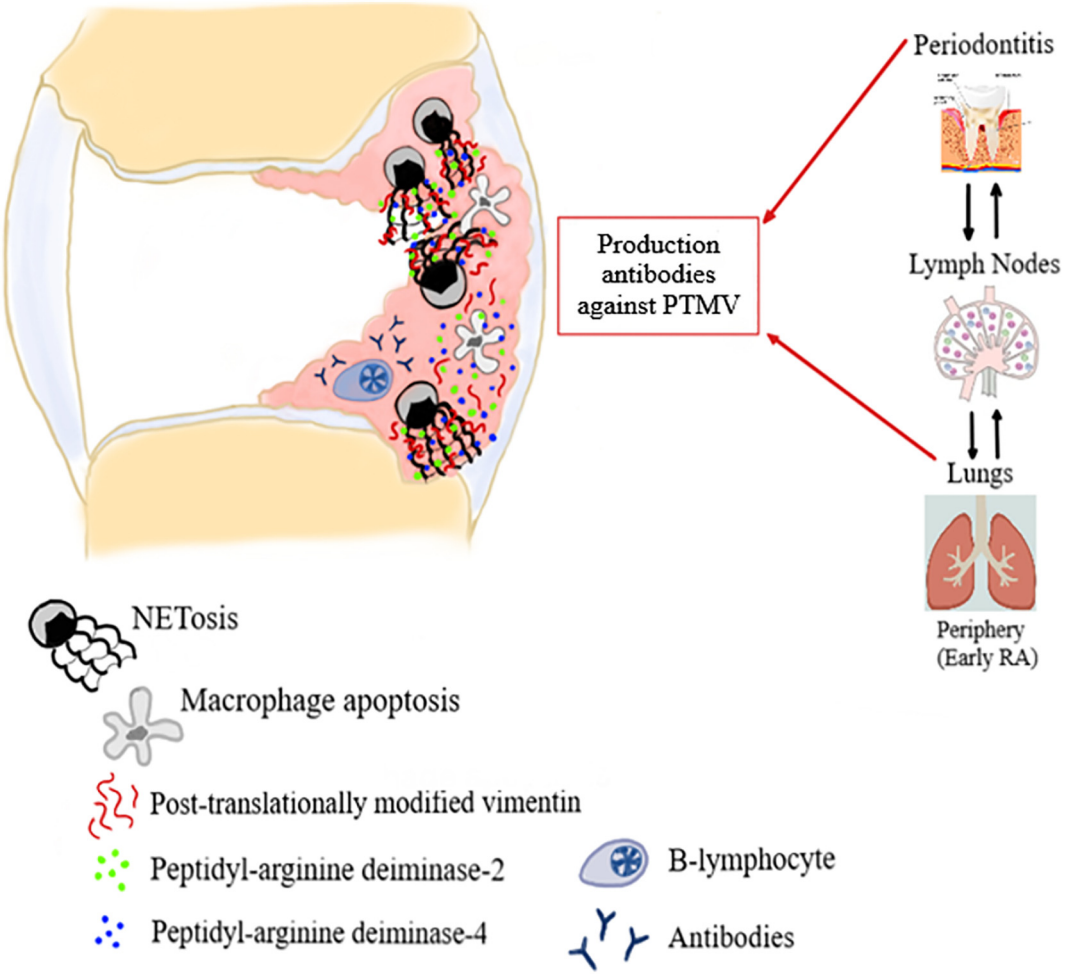

Fig. 3. Local production of post-translational modified vimentin in the synovium of RA patients. The figure illustrates a potential mechanism for the formation of post-translational modified vimentin (PTMV) that is closely related to neutrophilic inflammation. Macrophages and neutrophils migrating from the periphery express high levels of peptidyl-arginine deiminase-2 (PAD-2) and peptidyl-arginine deiminase-4 (PAD-4). PAD-2 and PAD-4 are involved in the citrullination of vimentin. The externalization of this enzymes and PTMV is due to apoptosis of macrophages and NETosis of neutrophils. Production of antibodies against PTMV is triggered by local inflammation in smoking and periodontitis. Lately formation of antibodies to PTMV takes place in the pannus of the affected joint.

reorganisation, regulate dynamic subunits exchange and promote solubility. The main phosphorylation domains in vimentin molecule are Ser-4. 5er-6-9, Ser-38, Ser-4l, Ser-71-72, Ser-4l8, Ser-429 and Thr-456-457 [4]. Phosphorylation of the vimentin head leads to some increase in the distance between the dimers, thereby preventing attaching of tetramers to organized filaments. The number of enzymes including proteinkinase A and C, Aurora-B kinase, p21-activated kinase, AKT1, Cdk1, Cdk5, PPl and PP2A that are involved in phosphorylation of vimentin maintain the stability of vimentin filaments [19–21]. Phosphorylation of vimentin is also associated with a migration of immune and tumor cells, regulation of cell growth and tumorogenesis [22]. From other side ADP-ribosylation of vimentin is associated with inhibition of filament organization process [23].

Modification of vimentin by small ubiquitin-like modifier (SUMO) is also associated with filament assembly and changes in their solubility [24]. O-linked glycosylation is mediated by B-*N*-acetylglucosamine and O-GlcNActransferase. O-linked glycosylation regulates signaling events related to nutrient sensing and stress responses [25]. Thus, glycosylation of vimentin in neurons is associated with stability of the filaments by inhibiting phosphorylation. Citrullination is the process of replacing the amino acid arginine with citrulline by peptidyl- arginine deiminase (PAD). Citrullization of vimentin negatively affects stability of the filaments, and transforme the filaments network into amorphous clusters around the cell nucleus. It can occur during cell death and tissue inflammation. Tissue vimentin citrullination serves as a potential biomarker of the hepatic fibrosis and ankylosing spondyloarthritis [26, 27]. Immune reaction to citrullinated vimentin participates in the pathogenesis of rheumatoid arthritis [28]. Like other members of the family of intermediate filaments, vimentin can be ubiquitinated [30]. Sites for ubiquitination in proteins of intermediate filaments are not fully understood.

3. Post-translationally modified vimentin as an autoantigenic target in rheumatoid arthritis

Vimentin is one of the antigens involved in the pathogenesis of rheumatoid arthritis (RA). Generation of post-translationally modified vimentin *in vivo* can abolish primary immunotolerance and induce disease in susceptible host and drives autoimmune responses in inflamed RA joints. Naturally occurring citrullinated post-translationally modified vimentin known as «Sa antigen» in RA presents in many tissues and can be purified from the placenta [31]. Antibodies against Sa-antigen are very specific (96.9%) for RA and can be found in 30–36.6% patients with the disease [32]. Citrullination of vimentin and other proteins of the synovial membranes, including fibrin and alpha-enolase, leads to a synthesis of anti-citrullinated peptide antibodies (ACPA) that are recognized biomarkers for RA [33]. Enzymatic citrullination of vimentin *in vitro* produce modified citrullinated vimentin (MCV) that is

used as antigen for detection of antibodies in RA [34].

The presence of anti-MCV antibodies is strongly associated with the genes of HLA class II that contain “shared epitope” that is the sequence of amino acid in HLA molecules presumably responsible for ACPA presentation in the immune system [35]. Anti-MCV antibodies are found in patients with the alleles of DRB1*01 (except*0103), DRB1*04 and DRB1*10, also it was related with PTPN22 alleles and smoking [36]. Especially high affinity of HLA-DRB1*0401 to MCV related peptides was described [37]. Relationship between serology and risk factors of RA is even stronger in patients also positive for anti-cytrullinated alpha-enolase peptide 1 (CEP-1) antibodies [37].

Immunization of HLA-DR4-IE transgenic mice with citrullinated fibrinogen induces experimental arthritis and synthesis of antibodies that react with citrullinated vimentin [38]. Induction of antibodies against citrullinated epitopes is probably a T-helper dependent process that clearly demonstrates the importance of HLA DRB1 alleles. Naturally occurring citrullinated proteins like filaggrin did not induce proliferative T-cell responses of lymphocytes of peripheral blood of RA patients if presented by “the shared epitope” [39]. In contrast, citrullinated fibrinogen and citrullinated vimentin induced T-cell proliferation and interferon-gamma production in cultured RA T-cells [40].

There are also several pathological events that lead to an induction of antibodies directed against post-translationally modified vimentin. Brief of the pathogenesis is illustrated in the Fig. 3.

Local inflammation of synovial membranes can generate post-translationally modified vimentin that becomes the autoantigenic target. The presence of intracellular citrullinated antigens like vimentin and alpha-enolase can be detected in the synovial lining of RA joint and correlate with systemic ACPA level [41,42]. Vossenaar et al. [43] suggested that vimentin citrullination are associated with granulocyte and macrophage apoptosis that produces significant amounts on intracellular components including vimentin and also peptidyl- arginine deiminase-2 and peptidyl-arginine deiminase-4 enzymes that are involved in inflammatory citrullination [44]. Fragmented extracellular DNA in the synovial fluid indicates an apoptosis in RA synovium and high levels of PAD expression in joint correlated with a systemic inflammatory activity [33]. Vimentin can also be excreted by activated macrophages under the influence of TNF-a [12].

RA is characterized by a high neutrophil content in the synovial fluid that is typically over 2000 cells per μl. The number of neutrophils correlates with the concentrations of IL-8. A specific form of apoptosis of neutrophilic granulocytes generates neutrophilic extracellular traps (NET) that are expulsion of DNA-protein complexes and enzymes from the cell [45]. During NETosis externalization of vimentin and other intracellular constituents occurs together with peptidyl- arginine deiminase, myeloperoxidase, cathepsin G and other enzymes involved in proteolysis and post-translational modifications [46]. High level of NETosis in the peripheral blood can be found in RA in contrast to osteoarthritis and controls. NETosis also was found in synovial pannus, rheumatoid nodules and skin of RA patients and its severity correlates with ACPA, rheumatoid factor and other markers of systemic inflammation including CRP and ESR [47]. Oxidative stress is another result of ubiquitous NETosis. In fibroblast cell line *in vitro* oxidative stress induces an expression of post-translationally modified vimentin that are recognized by ACPA from synovial fluid of RA patients [48].

Smoking is strongly related to RA and apparently is involved in immunology of this disease [49]. In smokers immunohistochemical testing of bronchoalveolar lavage samples can detect high peptidyl-arginine deiminase-2 expression and prominent citrullination of different proteins [50]. Citrullinated and carbamylated vimentin but not alpha-enolase and fibrinogen can be found in lung tissue of smokers and patients with chronic obstructive pulmonary disease [51]. Rheumatoid factor and ACPA can be found in part of the patients with bronchiectasis [52,53].

Among the peptide fragments of MCV similar cit-vim 446–466 and cit-vim 440–445 peptides can be detected in synovial lining and lung tissue. Antibodies directed against cit-vim 435–455 peptide found in lung tissue can be detected in blood of RA patients who were positive for “the shared epitope”, containing alleles of HLA-DRB1 [54].

Periodontitis induced by *Porphyromonas gingivalis* is a recognized risk factor of RA. This condition is related to chronic inflammation that directly involves gums and underlaid osseous structures and characterized by NETosis [55]. *P. gingivalis* produces bacterial peptidyl-arginine deiminase enzyme that can citrullinate C-terminal arginine of different proteins [56]. Another microorganism related to periodontitis is *Actinobacillus actinomycetemcomitans* that can produce pore-forming protein called leukotoxin A [57]. Leukotoxin A increases Ca influx in human neutrophils, induces NETosis, activates peptidyl-arginine deiminase enzyme and lead to citrullination of vimentin that can be identified in periodontal cavity [58]. *Prevotella intermedia* can destroy NET by bacterial nucleases that leads to increased activity of the neutrophilic PAD [59].

ACPA and autoantibodies against post-translational modified vimentin (PTMV) are synthetized locally in synovial lining [60].Van Steendam et al. [61] found antibodies against citrullinated vimentin in immune complexes purified from synovial fluid of 11 of 12 ACPA positive RA patients. Measurements of the local production of rheumatoid factor and ACPA antibodies have shown a local production of autoantibodies in 48% of RA patients and were found in patients with high IL-8 levels and number of neutrophils in synovial fluid.

Carbamylated PTMV is another autoantigen in RA that represents modification of lysine residues resulted in homocytrulline formation. Thiocyanate found in cigarette smoke is potential factor related to carbamylation. High level of tissue inflammation in smokers is the cause of myeloperoxidase production that can oxidase thiocyanate to cyanate. The same process happens during neutrophilic inflammation in synovial lining that induces formation of carbamylated PTMV [62].

In experimental mice models of smoking an increase of carbamylated PTMV and anti-carbamylated PTMV was detected. Although in human significant correlation between antibodies to carbamylated PTMV and smoking was not found [63]. Immunization of rabbits with carbamylated PTMV induced specific antibodies against the antigen, and also antibodies against Fc of IgG similar to human rheumatoid factor were also identified. Incidence of antibodies to carbamylated PTMV in RA varied from 28% to 78% [64, 65]. Antibodies to carbamylated PTMV were shown to be presented in 68.7% of ACPA positive patients but only in 3% of ACPA negative RA patients [66]. Detection of autoantibodies against carbamylated PTMV was related to SE containing alleles of HLA-DRB1 [67]. Although the presence of anti-MCV and anti-carbamylated PTMV antibodies is closely related, there were no cross-inhibition of binding of antibodies by alternative antigen [63]. Seropositivity against carbamylated proteins were detected in 16% ACPA negative RA cases characterized by aggressive course of disease, and the levels of the antibodies were not influenced by anti-B cell therapy [68].

Acetylation is another post-translation modification of PTMV that plays role in RA. Antibodies against acetylated PTMV of IgG class have specificity of 86.2% and can be identified in 36.6% of ACPA-positive patients and in 13.2% ACPA negative RA patients [66].

4. Antibodies against mutated citrullinated vimentin in diagnostic testing

Anti-mutated citrullinated vimentin antibodies (anti-MCV) are the member of big family of anti-citrullinated antibodies. It includes antibodies against naturally occurring citrullinated antigens like filaggrin (anti-keratin antibodies [69] and anti-perinuclear factor [70], or citrullinated vimentin (or Sa antigen) purified from placenta [71]. Another generation of the assays detects antibodies against recombinant antigens. Among them the most frequently employed anti-citrullinated antibodies are anti-cyclic citryllinated peptide antibodies (anti-CCP) and antibodies against MCV. There are several other commercially

Table 1
Clinical characteristics of different ACPA tests (results presented at 2014 Congress of Autoimmunity).

ACPA test	eRA (n = 37)	5yrRA (n = 36)	Specificity	Number of disease control	Combined specificity
aCCP2	61.7%	84.8%	91.8%	110	93.0
CCPlus	60.0%	n.d.	100%*	18	(9/128)
aCCPhs	66.0%	73.9%	89.3%	122	89.3
aMCV	76.6%	87.0%	89.2%	28	(16/150)

ACPA – anti-citrullinated peptide antibodies; aMCV – antibodies mutated citrillinated vimentin; aCCPhs – "high sensitive" anti-citrullinated cyclic peptide; eRA – early rheumatoid arthritis; 5yrRA – rheumatoid arthritis with 5 years duration. aCCPhs and aMCV (Orgentec Diagnostika, Mainz, Germany), aCCP2 (Euroimmun, Lubek Germany) and Immunoscan CCPlus (Euro-Diagnostica, Malmo, Sweden).

available assays for antibodies against different citrullinated proteins but they were not so intensively studied [72].

Original anti-MCV antibodies (Orgentec AG) are currently additional method for detection of antibodies to citrullinated antigens that was not included into the set of ACR/EULAR diagnostic criteria for RA in 2010 year. According to these diagnostic guidelines testing for ACPA suggests only anti-CCP testing. Anti-MCV antibodies have a sensitivity of 77–85% that is superior to anti-CCP antibodies but the specificity is 85–89% that is significantly less that of anti-CCP [73]. Anti-MCV can be found in several autoimmune diseases, especially psoriatic arthritis and systemic lupus erythematosus (SLE). Because of low specificity of anti-MCV antibodies, they do not add any additional information to anti-CCP testing in diagnosis of rheumatoid arthritis [74].

New anti-CCP hs (high sensitive)®test from Orgentec AG is based on three selected and optimized peptide epitopes from the body's own MCV protein. We compared the different tests for ACPA in patients with early RA and long-standing disease (Table 1). Although MCV is less useful for an early diagnosis of RA it can be used as additional laboratory biomarker for selection of patients for treatment with biologic agents. Seropositivity for anti-MCV antibodies was lower in responders to rituximab and also changed significantly in patients with good clinical response [75].

5. Autoantibodies against vimentin in sarcoidosis

Sarcoidosis is an inflammatory granulomatous systemic disease with enigmatic etiology. Non-caseous granulomas is the most specific feature of sarcoidosis that can be found in lung, lymphoid nodes, eyes and skin of patients. Composition of non-caseous granulomas includes antigen-presenting cells (macrophages, dendritic cells), debris of cells and CD4+ T-cells with unknown specificity of T-cell receptor (TCR) [76]. Today autoimmune theory of sarcoidosis pathogenesis is thought to be the most convincing, although many questions remain to be answered. Autoimmune targets in sarcoidosis still stay uncharacterized. Absence of consistent animal models that reflect mechanism of non-caseous granulomas formation also holds back progress in understanding of sarcoidosis pathogenesis.

There are many studies dedicated to searching for sarcoidosis-associated autoantigens. Research group of Häggmark et al. [77] showed that sera of nearly all the patients with sarcoidosis were reactive against one of the antigens in microarray built on 3072 protein fragments. Also, additionally, four proteins were proposed as sarcoidosis-associated autoimmune targets: ZNF688, MRPL43, NCOA2, ARFGAP1. Using 1D-SDS-PAGE and 2D-DIGE methodologies Eberhardt et al. [78] showed that 3 proteins can elicit the Kveim reaction in patients with sarcoidosis: tubulin, alpha-actinin-4, vimentin. Moreover, increased expression of vimentin was identified in the spleen of patients with sarcoidosis. Vimentin also induces hypersecretion of IFN-γ and TNF-α by peripheral blood mononuclear cells (PBMCs) of sarcoidosis patients. It should be noted that vimentin does not induce cytokines hypersecretion by PBMCs of patients with tuberculosis and healthy donors. Vimentin also was revealed to be aggregated in multinucleated giant cells [79]. Hypothesis that vimentin can be sarcoidosis-associated autoantigen was also substantiated by HLA haplotypes of patients with that nosology [80]. The research groups of Wahlström and Grunewald pointed out that more than half of the patients with sarcoidosis carried HLA-DRB1*03 allele [81]. This HLA type has high binding capacity for T-cell receptor Vα2.3+ and Vβ22+ [82–84]. They were also able to show that vimentin specifically binds to HLA- DRB1*0301 and Vα2.3+ and Vβ22+, but not to other type of HLA and TCR receptors [85]. Also, synthesized protein V (Vim429–443: DSLPLVDTHSKRTLL), that resembles main antigenic binding epitope of vimentin, induces active secretion of INF-y by PBMCs, extracted from HLA-DRB1*0301 positive patients with sarcoidosis [85]. Clonal expansion of Vβ22+ Vα2.3+ CD4+ T-cells were identified in all HLA-DRB1*0301positive patients with sarcoidosis, but not in patients with other HLA genotypes. Additionally, the possible role of vimentin in pathogenesis of sarcoidosis was substantiated by high prevalence (33,3%) of anti-MCV antibodies in angiotensin-converting enzyme (ACE) positive patients with sarcoidosis (unpublished results by Lapin S., Strashinova A., Zinchenko J.). Data about sarcoidosis-associated autoantigens are scarce, but the present results point to sarcoidosis as a disease with autoimmune reactions to multiple autoantigens that are deeply influenced by HLA genotype. Vimentin is the most promising autoimmune target in a specific HLA group of patients with sarcoidosis.

6. Autoimmune reactions to vimentin in systemic lupus erythematous

There are two types of kidney damage in lupus nephritis: glomerulonephritis and tubulointerstitial inflammation. Tertiary lymphoid structures are tissue formations that are found in damaged kidney interstitium and determine the severity of tubulointerstitial inflammation. These structures consist of contoured germinal and plasmoblastic centers, and T and B-cell aggregates [86]. Oligoclonal CD4+ T-cells and the presence of expansion and clonal selection of B-cells due to the presence of an autoantigen was detected in tubulointerstitial inflammation [87]. Kinloch et al. [88] demonstrated presence of autoantibodies against the cytoplasmic components of cells in biopsy of kidney of patients with SLE. Further, with the help of mass spectrometry, vimentin was identified to be a target of cytoplasmic antibodies in 6 of 8 patients. It is worth to note that autoantibodies located in tubulointerstitial spaces differ from serum circulating autoantibodies in SLE patients [89]. Inflammation in the interstitial spaces of kidney results in apoptosis of macrophages and degradation of components of the cytoskeleton. Increased expression of vimentin on the cell surface was observed [90]. Moreover, during inflammation, vimentin is expressed by damaged endothelial and epithelial cells of the renal tubules [91]. High titers of anti-vimentin antibodies are associated with severe tubulointerstitial inflammation in SLE patients. Since antibodies are deposited in the local inflammation focus, the complement system is activated, which leads to increased inflammation, destruction of the tissue and fibrosis of the renal tissue.

Glomerulonephritis in SLE is caused by the deposition of anti-dsDNA antibodies in the glomeruli [92]. André-Schwartz and colleagues [93] revealed the ability of monoclonal anti-DNA lupus autoantibodies to bind to vimentin. Bruschi et al. [94] has indicated that glomerular antibodies react against 11 proteins, including vimentin, but the antibody reactivity was directed mainly against a-Enolase and Annexin.

7. Vimentin and antiphospholipid syndrome

Antiphospholipid antibodies are family of autoantibodies directed

against phospholipids and phospholipid-binding protein. Their presence clinically linked with thrombosis and reccurent miscarriages. Antibodies to cardiolipin (aCL), ß2glycoprotein-I (aß2GPI) and lupus anticoagulant were included in the laboratory criteria for antiphospholipid syndrome (APS).

Thebault et al. [95] demonstrated that vimentin and cardiolipin can interact on the surface of apoptotic cells and form an immunogenic structures. Vimentin can bind to cardiolipin by electrostatic interaction between the positively charged amino acids of vimentin and the negative charge of cardiolipin [96,97]. Ortona and colleagues have showed, that antibodies against the vimentin/cardiolipin complex (aaVC) were found in 55,2% of patients that were negative and in 92.5% of patients that were positive for aCL and aß2GPI [96]. Another study by Conti et al. [98] detected aaVC in 45.8% of seronegative patients with clinical profile suggestive of APS and in 88% of patients that were positive for aCL and aß2GPI. According to this data, vimentin can serve as co-factor protein for aCL. It was found that the presence of aaVC is highly specific marker for prediction of arterial and venous thromboses [99]. Thus, aaVC may be useful tool for diagnosis of seronegative APS patients.

Meanwhile aaVC are also involved in coagulation cascade. Procoagulant mechanism is due to the binding of the antibodies to leukocytes that resulted in the release of a platelet activating factor and other pro-thrombotic factors [100]. Binding of aaVC to endothelial cell also induce phosphorylation of interleukin receptor-associated kinase (IRAK) and activation nuclear factor kappa B (NF-kB) with the subsequent release of pro-inflammatory and pro-coagulating factors [101]. It should be emphasized that aaVC is non-specific for APS, as these antibodies were detected in 43.3% of the patients with SLE and in 16.6% of the patients with RA [96]. Additionally, anti-MCV antibodies were found in 26.6% of patients with APS [99]. A statistically significant correlation between the titers of anti-MCV antibodies and aaVC in serum was found.

8. Vimentin in pathogenesis of other autoimmune conditions: Crohn's disease, ankylosing spondyloarthritis, idiopathic pulmonary fibrosis

Crohn's disease (CD) and ulcerative colitis (UC) are chronic, relapsing, idiopathic disorders of the gastrointestinal tract. CD is characterized by immune, transmural, segmental, granulomatous inflammation of the gastrointestinal system of various localization from the oral cavity to the anus, with the development of local and systemic complications, whereas the UC - by affecting only the colon with the obligatory involvement of the rectum [102]. Frequently, these diseases have overlapping and nonspecific clinical and histologic characteristics. Therefore, it is necessary to search for potential biomarkers in order to confirm the diagnosis. Mor-Vaknin [103] demonstrated that vimentin takes part in the pathogenesis of CD and UC. Comparing mice with a knockout vimentin gene and wild-type mice, less inflammation develops in knockout animals. In CD and UC an increased expression of metalloproteinases (MMP) that lead to tissue remodeling was identified. Since MMP-2 and -8 take part in the destruction of vimentin it is worth to note that MMP-2 is generated by activated macrophages, which form granuloma in Crohn's disease [104]. Høg Mortensen et al. [105] showed that citrullinated and MMP-degraded vimentin in serum is specific marker for Crohn's disease. Patients with high level of citrullinated and MMP-degraded vimentin are 5.62 times more likely to have Crohn's disease rather than ulcerative colitis. Specificity of that marker for CD was 78%.

The citrullinated and MMP-degraded vimentin level in sera of patients with ankylosing spondyloarthritis was significantly higher than in serum of a healthy control. Bay-Jensen and colleagues [106] showed that these form of vimentin could be a prognostic marker for ankylosing spondyloarthritis. Citrullinated and MMP-degraded vimentin level was also raised in RA. A high level of the protein is associated with the more severe ankylosing spondyloarthritis, since 67% of patients had a radiographic progression. Moreover, anti-MCV antibodies were detected in 37% of patients with ankylosing spondyloarthritis [107].

Vimentin plays a role in the pathogenesis of autoimmune reactions in idiopathic pulmonary fibrosis. Aggregates of B cells around specific fibroblastic foci are observed inidiopathic pulmonary fibrosis [108]. Vimentin causes HLA-DR-dependent increased *in vitro* proliferation of CD4 + cells, which was taken from the blood of patients with idiopathic pulmonary fibrosis. Increased production of IL-4, IL-17, and TGF-β1 cytokines by T-lymphocytes was also noted. Furthermore, TGF-β1 increases the secretion of vimentin by endothelial cells [109]. Jun Li et al. [110] observed a high concentration of vimentin in the exhaled breath condensate and blood plasma in patients with idiopathic pulmonary fibrosis. Comparing idiopathic pulmonary fibrosis with chronic obstructive pulmonary disease and healthy control sera, a high titer of anti-vimentin IgG antibodies was observed in idiopathic pulmonary fibrosis. The level of anti-vimentin antibodies in patients with idiopathic pulmonary fibrosis was inversely correlated with the physiological measurements of lung function. The most unfavorable prognosis was observed in patients with the highest anti-vimentin antibody levels.

9. Conclusion

Vimentin is a ubiquitously distributed protein of the intermediate filament family. Post-translational modifications influence not only structural and conformational features of vimentin molecules, but also play role in pathogenesis of inflammatory and autoimmune disorders. Native and post-translational modified vimentin can be secreted by immune cells on their surface, which leads to the appearance of a target for the synthesis of antibodies. Modified forms of vimentin are associated with inflammation. NETosis plays important role in the secretion of modified vimentin in RA. The participation of NETosis is noted in the pathogenesis of many autoimmune diseases and, probably, there can also be a secretion of this protein.

It was shown that generations of PTMV are profoundly involved in the pathogenesis of RA, can induce disease in susceptible hosts and linked with specific HLA genotypes. Citrullination is usually induced by smoking, increased apoptosis of macrophages and granulocytes, NETosis and chronic inflammatory processes and performed by peptidyl-arginine deiminases. Citrullinated vimentin can be detected in the lung, sinovium and sera of RA patients. Local and systemic concentrations of antibodies to vimentin in RA patients correlate with the activity of disease, concentrations of IL-8 and count of neutrophils in the synovia. Carbamylation of vimentin is also induced by neutrophilic activation. The synthesis of autoantibodies to carbamylated vimentin is deeply linked to anti-citrullinated vimentin antibodies, but there was no cross-inhibition between the antibodies. Antibodies to acetylated vimentin have high specificity in RA patients.

Identification of phenomena of increased production of anti-citrullinated proteins antibodies leads to creation of recognized biomarker of RA, that are anti-cyclic citrullinated peptide antibodies and modified citrullinated vimentin. Antibodies to modified citrullinated vimentin have a high sensitivity, but can be found in another autoimmune diseases.

The pathogenesis of sarcoidosis is remained to be clarified, but today autoimmune hypothesis is one of the most convincing. In sarcoidosis, epitopes of vimentin were identified to be antigenic targets in cohort of patients with HLA-DRB1*0301 alleles. Vimentin in sarcoidosis patients also induces increased secretion of pro-inflammatory cytokines and clonal expansion of lymphocytes.

Systemic lupus erythematosus is a systemic autoimmune disease that is notoriously known for a wide spectrum of autoimmune targets. Antibodies to vimentin were identified in serum and tubulointerstitial kidney spaces and their high concentration associated with severe kidney damage. Moreover, antibodies to double strand DNA cross-reacted with vimentin molecules. In antiphospholipid syndrome vimentin

interacts with cardiolipin and induces a synthesis of pro-trombogenic antibodies, that have a high prevalence in patients seronegative for antibodies to cardiolipin and ß2glycoprotein-I.

Increased concentration of post-translational modified vimentin was also identified in Crohn's disease, idiopathic pulmonary fibrosis and ankylosing spondyloarthritis.

Native and post-translational modified vimentin is involved in the pathogenesis of a wide spectrum disorders. Modifications of protein structure lead to the creation of new highly antigenic epitopes that induce synthesis of autoantibodies. Today, antibodies to modified citrullinated vimentin become an important diagnostic and prognostic marker for patients with rheumatologic disorders. Emergence of new data about participation of vimentin in the pathogenesis of other systemic diseases make research in this field.

Conflict of interest

The authors declare no conflicts of interest, including any financial and personal relationships with other people or organizations that could have inappropriately influenced this work.

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