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# Role of Serum Tubulin Alpha 1C in Pathogenesis of Inflammation

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**Abstract:**

**Background:** The alpha/beta-tubulin heterodimer is the structural subunit of microtubules. They share 40% amino acid sequence identity, exist in several isotype forms.Tubulin-α1-C, also known as tubulin alpha-6, is one of the alpha-tubulin family members. There are three different isoforms of tubulin-α1-C in human tissues, tubulin-α1-C isoform a, b, and c. Tubulin-α-1c might bind to its antigen on cell surface and induce inflammatory response and exacerbate tissue damage. Binding of the Tubulin-α-1 tubulin to epithelial cells resulted in the increased expression of TCF5, which induced downstream proinflammatory cytokines such as VEGF and sustained local tissue inflammation.

**Objective:** find out the role of serum tubulin alpha-1c in pathogenesis of inflammation and might be a novel biomarker with promising sensitivity and specificity in inflammation.

**Methods:** The systematic literature review was performed using The PubMed, Google Scholar, Science Direct and the Medline for information on tubulin alpha-1c identification and its role in inflammation between 2006 and 2022 was included, The authors also evaluated references from relevant literature. Documents were in English, and unpublished manuscripts, oral presentations, and conference abstracts were excluded because they were not related to important scientific studies.

**Conclusion:** our results concluded that tubulin-α-1c has an important role in the pathogenesis of inflammation and may be used in the future as marker of inflammation. long term follow up is required to identify the role of tubulin-α-1c and confirm whether it can be used as a predictor of inflammation.

**Keywords:** Tubulin Alpha 1C, Inflammation, Microtubules.

## Introduction:

Microtubules are cytoskeletal filaments that are dynamically assembled from α/β-tubulin heterodimers and are basic structural components of various vascular cells **(1).**

The tubulin superfamily includes six distinct families, the alpha-, beta, gamma-, delta-, epsilon-tubulins, and zeta-tubulin. The alpha- and beta-tubulins are the major components of microtubules, while gamma-tubulin plays a major role in the nucleation of microtubule assembly. The delta- and epsilon-tubulins are widespread but not ubiquitous among eukaryotes **(2).**

The alpha/beta-tubulin heterodimer is the structural subunit of microtubules. They share 40% amino acid sequence identity, exist in several isotype forms, and undergo a variety of posttranslational modifications. The structures of alpha- and beta-tubulin are nearly identical. Tubulin-α-1C, also known as tubulin alpha-6, is one of the alpha-tubulin family members and is ubiquitously expressed in 27 tissues including bone marrow **(2).**

There are three different isoforms of tubulin-α-1C in human tissues: tubulin-α-1C isoform a, b, and c. The expression variations of different tubulin-α-1C isoforms among different cell types are still elusive **(1).**

α-tubulin has been identified as an autoantigen in patients with chronic allograft rejection after lung transplantation and its autoantibodies contribute to bronchiolitis obliterans syndrome (BOS) following lung transplantation (**3).**

Microtubules (MTs) are involved in many important functions such as intracellular transport, cell division, cell motility, and morphogenesis. Functional adaptation of MTs is often achieved through posttranslational modifications **(4).**

Most tubulin modifications occur at the C-terminal tails, which are present on the MT surface where they provide the key interaction sites for MT-associated proteins (MAPs) and molecular motors. The most prevalent modifications are detyrosination, which consists in the removal of the very C-terminal tyrosine from α-tubulin resulting in the generation of the so-called αΔ1-tubulin, and polyglutamylation, which involves the addition of glutamate side chains to both tubulins **(4).**

Detyrosination was the first tubulin modification to be discovered and since then shown to regulate various MAPs and molecular motors. It acts as a positive regulator of kinesin-1 (Kif5B) and kinesin-7 (CENP-E) while it inhibits the activity of kinesin-13 and the binding of CAP-Gly domain–containing proteins such as cytoplasmic linker protein of 170 kDa (CLIP170) and p150$^{Glued}$, a component of the dynein-dynactin complex **(5).**

Tubulin detyrosination plays an important regulatory role in cell division, cell migration, neuronal physiology, and cardiac mechanotransduction. Hence, this modification has been implicated in various disorders including cancer, cardiomyopathies, heart failure, and neurodegeneration **(6).**

The two members of the vasohibin family (VASH1 and VASH2) in complex with their essential cofactor small vasohibin-binding protein (SVBP) were shown to catalyze the removal of the tyrosine. The identification of VASHs revealed the existence of at least one additional tubulin detyrosinase. In contrast, the reverse reaction is catalyzed by a single enzyme called tubulin tyrosine ligase (TTL) **(7).**

Detyrosinated tubulin can be further processed by sequential removal of one or two glutamates, which is catalyzed by members of the cytosolic carboxypeptidase (CCP) family resulting in the formation of αΔ2- or αΔ3-tubulin. Apart from deglutamylation of the α-tubulin primary chain, CCPs also remove posttranslational polyglutamylation, which is added by members of the tubulin tyrosine ligase like (TTLL) family **(8).**

The human genome encodes nine glutamylases, among which six have autonomous activity, with TTLL4, TTLL5, and TTLL7 being involved mostly in the initiation while TTLL6, TTLL11 and TTLL13 are highly efficient at catalyzing the elongation of the glutamate side chains **(4).**

The remaining three glutamylases—TTLL1, TTLL2 and TTLL9—are inactive on their own, and they are most likely a part of larger complexes requiring other subunits for their activity as exemplified by TTLL1, which forms a complex with four additional proteins **(4).**

The removal of glutamyl side chains is also a two-step process. Among six CCP family members, most (CCP1 to CCP4 and CCP6) are involved in shortening the glutamate chain, while CCP5 specifically removes the branching point glutamates **(9).**

At the molecular level, polyglutamylation has been shown to regulate MT stability either by affecting the binding of classical MAPs such as MAP1, MAP, and tau or by controlling the activity of MT severing enzymes including spastin and katanin **(10).**

Moreover, this modification also regulates the activity of certain kinesins as well as cytoplasmic and ciliary dyneins **(11).** Dysregulation of polyglutamylation was found to be associated with several pathologies including neurodegeneration **(12)**, cancer progression, and various ciliopathies underlying the importance of maintaining proper levels of this modification **(13).**

The discovery of a family of tubulin-modifying enzymes composed of two members, TMCP1 and TMCP2, which catalyze the removal of amino acids from α- and β-tubulin C-terminal tails. TMCP1, which corresponds to the recently described enzyme called MT-associated tyrosine carboxypeptidase (MATCAP), is specific to α-tubulin and acts as a highly efficient detyrosinase. However, it also generates αΔ2-tubulin through sequential removal of tyrosine and glutamate **(14).**

In contrast, TMCP2 catalyzes primarily the modification of βI-tubulin from which it sequentially removes three residues generating a previously unknown βIΔ3 modification. Using newly developed modification-specific antibodies, we show that βIΔ3-tubulin is present on centrioles, mitotic spindles, and cilia in various cell lines of different origins suggesting that it may play a role in cell division and ciliogenesis **(4).**

**α-, β-, and γ-Tubulin, and Microtubule Formation:**

Human γ-tubulin is one of the five known tubulin members (γ-, α-, β-, ε-, and δ-tubulin) in the GTPase superfamily of tubulins. A common feature among the members is a conserved GTP-binding domain in the N-terminal region, which consists of five α-helices and six parallel β-strand, whereas the C-terminal region is most variable **(15).**

The α and β monomers of tubulin exist as isotypes differing in their amino acid sequence encoded by different genes. α/β heterodimers polymerize into microtubules, which are indispensable for cell division and growth. The expression of specific isotypes of tubulin is associated with cancer, but the molecular mechanisms behind this effect are still largely unknown **(16).**

The mutations of tubulin isotypes expressed in invasive tumors affect the binding of anti-cancer drugs and may contribute to drug resistance. Therefore, understanding the molecular mechanisms behind these effects will help to develop molecular targets for the design of novel anti-microtubular drugs **(16).**

Moreover, α/β-tubulins are post-translationally modified, and cell cycle or stress-driven signaling pathways also regulate microtubule dynamics through interactions with microtubule associated proteins (MAPs) including molecular motors **(16).**

Data on the cellular functions of tubulin isotypes and post-translational modifications in physiological and pathological conditions can provide further insights into novel and often unexpected functions of tubulin isotypes in cell division and differentiation. For example, it has been shown that βII-tubulin is involved in the development of several types of tumors such as neuroepithelial and brain tumors, as well as colon and prostate cancer **(16).**

Nuclear βII-tubulin is found in aggressive metastatic tumors, and its association with anti-microtubular drugs paclitaxel and vinblastine as well as presence in molecular forms has been suggested **(16).**

Similarly, cytoplasmic βII-tubulin not assembled into microtubules interacts with the voltage-dependent anion channel (VDAC), and this interaction has been found to play a bioenergetic role in muscle cells, while the interaction between βIII-tubulin and the VDAC is considered to play a major role in brain synaptosomes **(17).**

One of the most important mechanisms through which cells overcome the effects of anti-microtubular chemotherapeutic agents is their resistance to enter the apoptotic pathway. The inhibition of proteins with an anti-apoptotic function, which is often overproduced in tumors, may therefore improve the effect of anti-microtubular drugs **(18).**

The development of new drugs could involve the generation of derivatives of existing compounds which could endow them with a higher anticancer potential using state-of-the-art approaches based on a knowledge of molecular biology of tubulin structures in combination with computer-aided drug design, which has been demonstrated in one of the papers in this issue **(18).**

Tubulin also plays an important role in the nervous system, both in health and in neurodegenerative diseases such as Parkinson's and Alzheimer's. Mutations of αβ-tubulin dimers and γ-tubulin are behind brain malformation and are known to impair cognitive functions. Epilepsy presents another example of one of important tubulinopathies **(19).**

However, knowledge of tubulin mutations and neuroanatomical and behavioral defects connected to epilepsy is still limited and requires a major effort to elucidate it. The regulation of γ-tubulin containing nucleation centers for microtubule reorganization is important during mast cell activation **(20).**

However, besides microtubule nucleation, γ-tubulin also plays a major role in other cellular functions, as judged by the existence of numerous γ-tubulin interactions with nuclear proteins, which have been reported in both plants and animals. There are a growing number of bacterial tubulin-like proteins that are engaged in a wide range of cytoskeletal functions **(20).**

Importantly, the ability to assemble protofilaments and fibrillar structures characteristic of prokaryotic tubulins (e.g., FtsZ) is preserved in the case of eukaryotic tubulins including γ-tubulin. Several articles in this

Special Issue cover a broad area of tubulin biology mentioned above and enable a better understanding of the roles tubulins play both in health and disease **(21).**

Microtubules (MTs) are essential cytoskeletal filaments that underlie diverse processes in eukaryotes including mitosis, intracellular transport and axon formation. Despite their involvement in a wide range of contexts, their basic structure and intrinsically dynamic behavior are widely conserved **(22).**

They are long, hollow cylinders assembled from the protein tubulin, a heterodimer of α- and β-subunits **(Fig. 1).** Tubulin polymerizes in a head-to-tail manner, bestowing MTs with a polarity that facilitates the organization of MT structures, directed transport, force generation and other scenarios that require spatial fidelity **(23).**

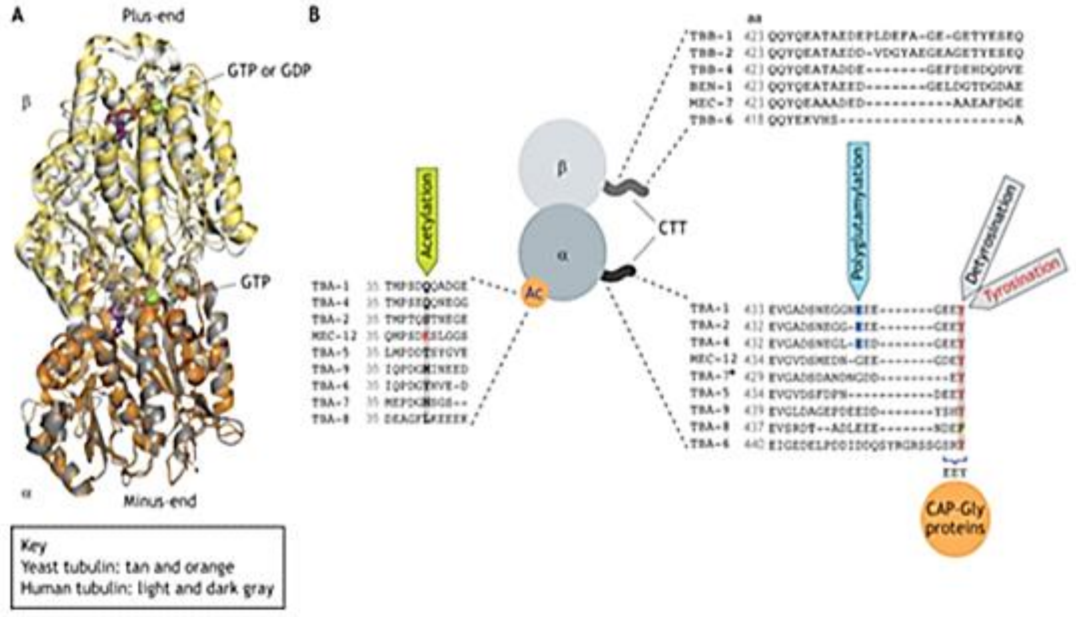

**Figure (1):** The tubulin structure **(22).**

Another conserved property, termed dynamic instability, is the propensity of MTs, driven by the hydrolysis of GTP bound to β-tubulin, to stochastically switch between periods of polymerization and depolymerization **(22).**

A key reason MTs can function in diverse roles is that their organization and dynamics can be spatially and temporally controlled by regulatory factors and MT-associated proteins (MAPs) **(24).**

Apart from the α-tubulin–β-tubulin heterodimer (α/β-tubulin), the tubulin family includes γ-tubulin, which is also ubiquitous and key for MT nucleation **(25)**. In addition, the specialized δ-, ε- and ζ-tubulins contribute to the structure and/or function of centrioles and basal bodies in a subset of eukaryotes **(26)**

**Microtubule diversity and the tubulin code:**

Despite the high conservation in MT structure and dynamic behavior, diversity is introduced at three levels. First, the tubulin family has undergone evolutionary expansion to produce multiple variants, or isotypes, of γ-tubulin in some species **(27)**, and α- and β-tubulin in most species **(28).**

Second, post-translational modifications (PTMs) can alter tubulin molecules and influence MT function, including their flexibility and stability Variation can also arise from altered expression of tubulin-modifying enzymes or the absence of PTM-target sites (modifiable amino acids such as glutamate, lysine and tyrosine) in specific isotypes **(fig.1) (29).**

Third, MT-associated activities such as polymerization, organization and directed transport can be controlled by MAPs and regulatory proteins **(24)**. Altogether these observations form the basis of the multi-tubulin or tubulin code hypotheses, which postulate specific contributions to MT function from isotype composition and/or PTMs. Work from many researchers has yielded impressive insights into tubulin structure, MT dynamics, PTMs, MAPs and regulatory proteins **(30).**

**Tubulin isotypes and the tubulin code:**

The role of tubulin isotypes in the functional diversity of the MT cytoskeleton has remained relatively unclear. One obstacle has been the difficulty in obtaining single-isotype tubulins for biochemical study. The formation of functional tubulin heterodimers requires a complex chaperone-mediated folding pathway **(22).**

Historically, successful exogenous expression in prokaryotic cells or overexpression in eukaryotic systems has not been reported. Until recently, single-isotype preparations were essentially limited to yeast tubulins and heterogeneous mammalian brain tubulins immuno-depleted of specific isotypes **(22).**

A second obstacle has been the entanglement of isotype-specific effects and secondary phenotypes in cell-based experiments. α/β-stoichiometry is one factor, as surplus β-tubulin can be toxic **(22).**

Another factor is assigning isotype contribution, as removal of one isotype can also change the relative ratios of the remaining subunits. Thus, interpretation of phenotypes following knockdown or overexpression of tubulin isotypes can be complicated **(31).**

Several advances are helping to unravel this longstanding mystery. First, improvements in gene editing and isotype replacements have begun to reveal the importance of individual isotypes in MT dynamics and spindle positioning **(31)**, cilia and flagella assembly, and neurogenesis **(32).**

Second, the successful purification of functional recombinant tubulin is beginning to yield insights into the biochemical properties of various isotypes **(33).** Combining these advances with insights from pathological tubulin variants will help to elucidate individual isotype function in specific cellular contexts **(34).**

**Anti-tubulin-α-1c role in inflammation:**

Tubulin is the basic unit of microtubules, which constitute parts of the cytoskeleton and form spindle fibers during cell division. There is evidence that autoantibodies to tubulin are present in the sera of normal mammals, including humans. These “natural” autoantibodies are generally present in low titers and are specific for tubulin **(3).**

Circulating immune complexes (CICs) present in peripheral blood contain a variety of antigens that may associate with underlying diseases. Autoantigens incorporated into CICs are promising candidates for diagnostic biomarker screening. potential BD autoantigens in CICs present in BD patients. A total of 17 novel potential autoantigens were identified from CICs of Behcet’s Disease **(35).**

The autoantibody against one of these autoantigens, tubulin-α-1c, it is a novel diagnostic biomarker with promising sensitivity and specificity in BD. The anti-tubulin-**α**-1c antibodies were associated with BD inflammation level and disease activity and participate in the pathogenesis of the disease **(36).**

Elevation of anti-tubulin-α-1C in SLE patients was associated with increased SLEDAI and incidence of cutaneous lesions including malar rash, skin rash, and oral ulcer. anti-tubulin-α-1C might form immune complex with released tubulin-α-1C, leading to immune complex deposition and subsequent amplified inflammatory response and tissue destruction **(3).**

A total of 17 potential autoantigens were identified in CICs of BD patients, including alpha-enolase, anti-streptococcal/anti-myosin immunoglobulin lambda light chain variable region, tubulin-α-1c, It is noteworthy that these antigens were involved in physiological process including immune response, cell structure integrity, coagulation cascade, which implicated that the corresponding autoantibodies against these antigens might interfere these physiological process above and lead to cell/tissue damages or pathogenic abnormalities in these process **(36).**

It is generally believed that generation of autoantibodies is critical for development of many autoimmune diseases. However, unlike many autoimmune diseases, BD cannot be definitively diagnosed using those commonly detected autoantibodies in autoimmune vasculitis, such as antinuclear antibody (ANA) or anti-neutrophil cytoplasmic antibodies (ANCA). But anti-endothelial cell autoantibody (AECA) contributed to the vascular damage of BD **(37).**

Tubulin-α-1c has also been shown to promote aerobic glycolysis by upregulating YAP expression to promote aerobic glycolysis and enhance lactate metabolism, glucose consumption, and cell growth, migration, and invasion.

Tubulin-α-1c plays a significant role in the cell cycle and immune microenvironment in lung adenocarcinoma (LUAD). Elevated expression of tubulin-α-1c was correlated with poor outcome and with 13 tumour-infiltrating immune cells (TIICs) in LUAD . tubulin-α-1c was found to be upregulated in hepatocellular carcinoma (HCC) and pancreatic ductal adenocarcinoma (PDAC).

The antibodies against the K-α-1 tubulin which is highly homologous to tubulin-α-1c could be defined in human lung transplant recipients undergoing bronchiolitis obliterans syndrome (BOS). These antibodies bound to endothelial cells and the specific ligation results in increased expression of fibrogenic growth factors, activation of cell cycle signaling and fibro-proliferation **(38).**

Tubulins mainly play their physiological roles in cellular structure maintenance, GTPase activity and intracellular movement as components of cytoskeleton **(39).** Earlier studies have identified autoantibodies against K-α-1 tubulin and implicated that this protein could reach cell surface and was immunogenic under specific circumstances (**40**). Tubulin-α-1c might stimulate the expression of VEGF and damage endothelial cells in vasculitis and thrombosis **(41).**

The deposition of immune complexes, which were formed by vascular autoantigens such as histones, ribosomes, fibronectin, etc. and their autoantibodies, were able to cause vascular inflammation, and lead to exacerbated local inflammation within vascular endothelium **(36).**

Anti-tubulin-α-1c might also bind to its antigen on vascular cells and induce inflammatory response and exacerbate tissue damage. Binding of the anti-K-α-1 tubulin to epithelial cells resulted in the increased expression of TCF5, which induced downstream proinflammatory cytokines such as VEGF and sustained local tissue inflammation **(43).**

Elevation of anti-tubulin-α-1C in SLE patients was associated with increased SLEDAI and incidence of cutaneous lesions including malar rash, skin rash, and oral ulcer

The over-elevation of serum anti-tubulin-α-1C autoantibody in SLE was associated with higher disease activity and increased incidence of vasculitis manifestations, mainly cutaneous lesions. This autoantibody may become a novel biomarker of SLE vasculitis activity **(3).**

Elevated levels of serum anti-tubulin autoantibodies have also been reported to be associated with other organ-specific autoimmune diseases including Graves' disease, Hashimoto's thyroiditis, and demyelinating disease **(3).**

Binding of the anti-K-α-1 tubulin to epithelial cells resulted in the increased expression of TCF5, a transcription factor involved in the regulation of inflammatory response genes and fibro-proliferation cascade. The increased levels of TCF5 and c-Myc induced expression of downstream proinflammatory effectors such as VEGF, which initiated and sustained local tissue inflammation **(44).**

## Conclusion:

our results concluded that tubulin-α-1c has an important role in the pathogenesis of inflammation and may be used in the future as marker of inflammation. our study has some limitations, additional studies on serum tubulin-α-1c and long term follow up is required to identify the role of tubulin-α-1c in the pathogenesis of inflammation and confirm whether it can be used as a predictor of inflammation.

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