Granulomatosis with Polyangiitis (Wegener’s): An Alternative Name for Wegener’s Granulomatosis


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The Boards of Directors of the American College of Rheumatology, the American Society of Nephrology, and the European League Against Rheumatism recommend a gradual shift from honorific eponyms to disease-descriptive or etiology-based nomenclature.

The leadership of these three organizations tasked an international group of senior academicians who are experts in the care of patients with vasculitis and engaged in research in the field to provide the medical community with proper descriptive terms instead of the names for Wegener’s granulomatosis, Churg-Strauss syndrome, and Behçet’s syndrome. The move toward a vasculitis terminology based on pathology, rather than historical reference, was triggered by evidence that Dr. Friedrich Wegener was an army officer before and during World War II.1

As the first step towards a vasculitis nomenclature that is free of eponyms, the authors of this article met on November 7, 2010, and reached consensus on an alternative name for Wegener’s granulomatosis. As physicians whose clinical and research work focuses on vasculitis, we represent the diverse opinions of our international colleagues within the multiple medical specialties that have strong interests in vasculitis. This article announces the newly proposed name, outlines the reasons for seeking a new disease name, and explains the rationale for the proposed name.

The alternative name for Wegener’s granulomatosis is granulomatosis with polyangiitis (Wegener’s), which can be abbreviated as GPA. The parenthetical reference to Wegener’s will be phased out after several years, as the new usage becomes more widely known.

Granulomatosis with polyangiitis was initially described by Klinger in 1931 as variant of polyarteritis nodosa, and then in greater detail as a separate syndrome by Wegener in two articles appearing in 1936 and 1939.2–4 The term Wegener’s granulomatosis was introduced into the English-language literature by Drs. Godman and Churg in 1954.5 Granulomatosis with polyangiitis has previously been proposed as an alternative name for Wegener’s granulomatosis.6

We recognize the difficulty inherent in seeking a replacement term for a long-established disease name for this complex multisystem illness with highly variable clinical presentations. Although this replacement term is neither perfect nor encompasses all aspects of the pathophysiology and clinical spectrum of the disease, the new term is nonetheless fit for the intended purpose for several important reasons: inclusion of the word granulomatosis means that the new name recognizes the history of the disease name as well as a main feature of the pathology, and the word polyangiitis both reflects the frequent vasculitic involvement of multiple types of vessels and retains the nomenclature used by the Chapel Hill Consensus Conference for vasculitic involvement in a related condition called microscopic polyangiitis.7 The new term will not preclude its incorporation into a more detailed revised nomenclature and classification scheme for the vasculitides that may be developed in the future.

Finally, we propose inclusion of the parenthetical term (Wegener’s) for several years to help smooth the adoption of the new name, avoid confusion in the medical literature, and facilitate electronic searches.

Changing a name for a disease is never easy. We believe that the wider medical and patient communities will accept and adopt the use of granulomatosis with polyangiitis (Wegener’s) with the same spirit of international and multispecialty cooperation that led to our arriving at the new name.

DISCLOSURES

None.
Tolloid-like Proteinases Orchestrate Extracellular Matrix Formation

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Purification of osteogenic activity initially isolated bone morphogenic proteins (BMPs) 1 through 7 from bone extracts.1 BMPs 2 through 7 are members of the TGF-β superfamily, and on the basis of sequence homology, more than 30 TGF-β-like BMPs have been identified.1 In contrast, despite its name, BMP1 does not belong to the TGF-β superfamily because it differs structurally from other BMPs.2 Rather, BMP1 has procollagen C-proteinase (PCP) activity responsible for removing C-propeptides from procollagen types I through III.3 Consequently, BMP1 is the prototype of a group of proteinases, referred to as Tolloid (TLD)-like proteinases, that are conserved in species ranging from fish to humans.2

Four mammalian TLD-like proteinases have been identified so far, which include BMP1, mammalian TLD (mTLD; also called BMP1-3) that is encoded by alternatively spliced mRNA produced by the Bmp1 gene, and mammalian TLD-like 1 and 2. Bmp1 null mice, which lack BMP1 and mTLD, show a mild dorsal-ventral patterning defect and abnormal collagen fibrillogenesis and bone formation,4 possibly as a result of failure to cleave a BMP antagonist, Chordin, and deficient extracellular matrix (ECM) formation, respectively.

Collagen types I through III are synthesized as procollagens with N- and C-terminal propeptides. Removal of these propeptides by the PCP activity of TLD-like proteinases is essential for their maturation through self-assembly into fibrillar collagens.5 In addition, TLD-like proteinases process noncollagenous ECM components such as perlecan and small leucine-rich proteoglycans (SLRPs). Perlecan is a large proteoglycan that is a major component of basement membranes. The C-terminal motif of Perlecan promotes apoptosis resistance in fibroblasts through interactions with α2β1 integrins when removed from perlecan by TLD-like proteinases.2,6 SLRPs such as biglycan and decorin are synthesized as precursors,4 and biglycan and prodecorin are processed by TLD-like proteinases into the mature proteoglycans.2,7

Although biglycan and decorin modulate collagen fibrillogenesis as well as the bioactivity of various members of the TGF-β superfamily,6 their processing is thought to be another mechanism by which TLD-like proteinases regulate ECM formation. Because biglycan is located in the pericellular ECM, whereas decorin is more abundant in the interstitial ECM, biglycan may be responsible for the sequestration of TGF-β to cell-surface receptors, promoting ECM formation. In contrast, decorin may sequester TGF-β away from the cell surface to inhibit its receptor binding, suppressing ECM formation.6 TGF-β induces a net increase in ECM formation in development, tissue repair, and fibrosis by inhibiting expression of ECM-degrading proteinases. TGF-β also increases expression of ECM components, lysyl oxidase, and proteinases such as TLD-like proteinases that process ECM components and lysyl oxidase into their mature forms.2 Most TGF-β is secreted as a large latent complex (LLC), composed of latent TGF-β–binding protein (LTBP), and small latent complex (SLC), formed by TGF-β and latency associated peptide (LAP).9 SLC is disulfide-bonded to LTBP through LAP, and LLC is covalently bound to the ECM by LTBP. TGF-β can be activated through removing LAP by metalloproteinases (MMPs) or through interactions with thrombospondin or integrins. Although TLD-like proteinases do not remove LAP, they cleave LTBP to liberate LLCs from the ECM,9 rendering LAP susceptible to cleavage by MMPs with subsequent TGF-β activation. TGF-β activation by TLD-like proteinases and MMPs can also be upregulated by TGF-β. In addition, TGF-β can induce expression of probiglycan, which is then activated by TLD-like proteinases and promotes TGF-β’s binding to their receptors. Therefore, TLD-like proteinases complete a positive feedback loop in ECM formation.

JASN, Grgurevic et al.10 report that BMP1-3/mTLD is detectable in plasma of patients with chronic kidney disease (CKD), which suggests for the first time a profibrotic role for BMP1-3/mTLD in CKD. The authors found that administration of recombinant BMP1-3/mTLD increased whereas its neutralizing antibody reduced renal fibrosis in rats with subtotal renal ablation.

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