Proteoglycan form and function: A comprehensive nomenclature of proteoglycans

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Abstract

We provide a comprehensive classification of the proteoglycan gene families and respective protein cores. This updated nomenclature is based on three criteria: Cellular and subcellular location, overall gene/protein homology, and the utilization of specific protein modules within their respective protein cores. These three signatures were utilized to design four major classes of proteoglycans with distinct forms and functions: the intracellular, cell-surface, pericellular and extracellular proteoglycans. The proposed nomenclature encompasses forty-three distinct proteoglycan-encoding genes and many alternatively-spliced variants. The biological functions of these four proteoglycan families are critically assessed in development, cancer and angiogenesis, and in various acquired and genetic diseases where their expression is aberrant.
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Introduction

It has been nearly 20 years since the original publication of a comprehensive classification of proteoglycan gene families [1]. For the most part, these classes have been widely accepted. However, a broad and current taxonomy of the various proteoglycan gene families and their products is not available. In contrast to the classification of glycosaminoglycans (GAGs), primarily based on the chemical structure of their repeating disaccharide units, classifying proteoglycans is a much more complex task [2]. We propose a comprehensive and simplified nomenclature of proteoglycans based on three criteria including: Cellular and subcellular location, overall gene/protein homology, and the presence of specific protein modules within their respective protein cores. Whereas the first two attributes have been utilized in the past for various nomenclatures, the third attribute is of more recent development and represents a sort of "intrinsic signature" for various protein cores. Indeed, modular design is based on the simple concept that protein cores are made up of finite units, like pieces of Lego. The units represent a minimum level of organization and a module can be thought of as a functional domain that affects cell–matrix dynamics. Another key feature is that each module/functional unit can be stable and can fold on its own, without being part of the large precursor protein. Thus, a module is a self-contained component. An example of this is the LG3 domain of endorepellin, the C-terminal globular-like domain of perlecan, which has recently been crystallized [3]. Below, we will critically assess the field of proteoglycans which now encompass forty three distinct genes and a much higher number of proteoglycans due to alternative splicing, thereby providing a very rich and biologically-active group of molecules. As hyaluronan and the enzymes involved in the synthesis and degradation of various GAGs are not covered in this review, readers are referred to recent reviews covering these closely-related subjects [4–18].

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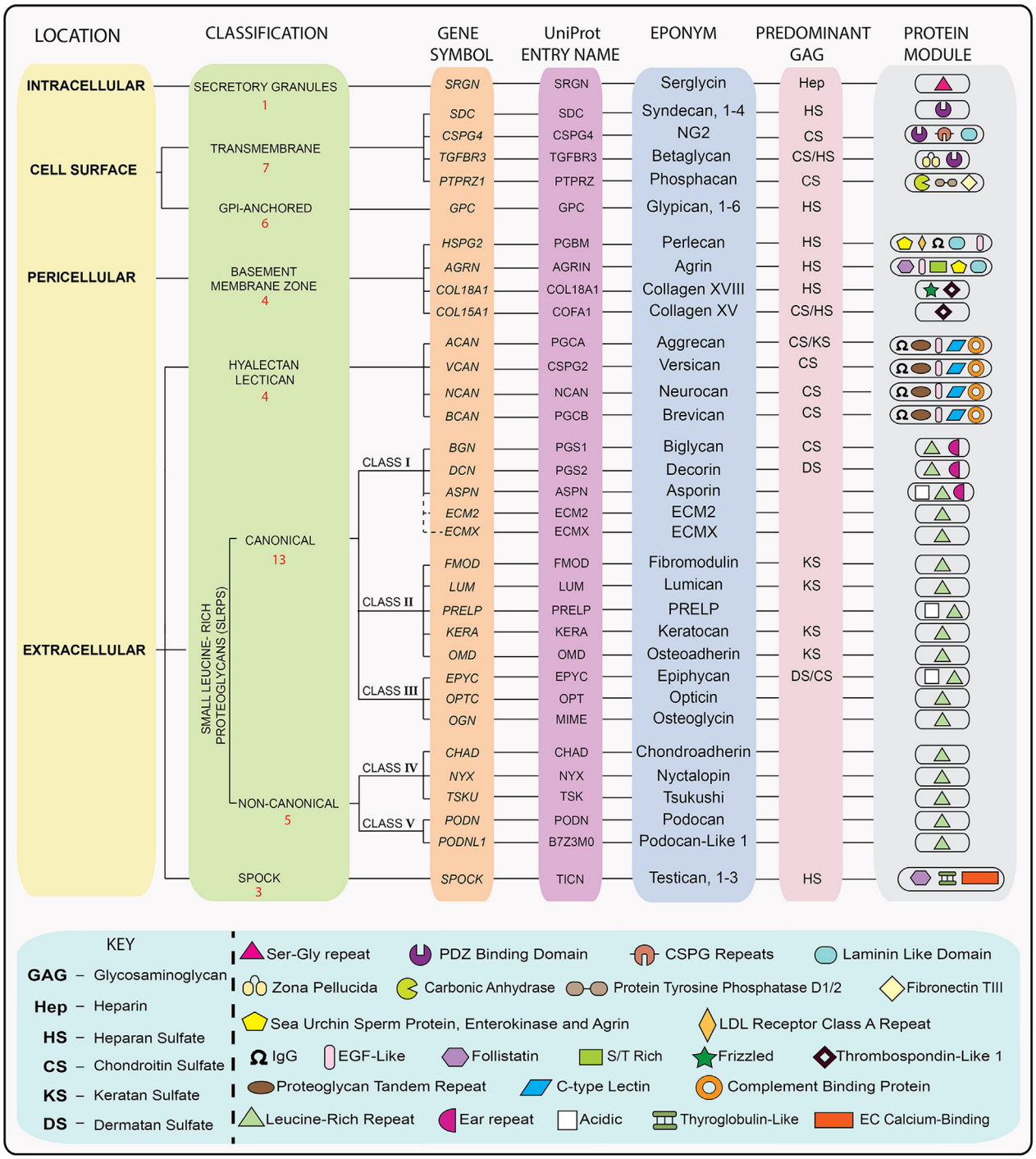

Fig. 1. A comprehensive classification of proteoglycans. The four families are based on their cellular and subcellular location, homology at the protein and genomic levels and the presence of unique protein modules which are often shared by members of a given class. The key for the various modules is provided in the bottom panel. For additional details about structure and function, please consult the text.

General features

Four major proteoglycan classes encompass nearly all the known proteoglycans of the mammalian genome (Fig. 1). Observing the types of proteoglycans based on cellular and subcellular localization, we can see that there is only one intracellular proteoglycan, serglycin. This unique proteoglycan forms a class on its own as it is the only proteoglycan that carries heparin side chains.

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