

The Role of Proteoglycans in Overgrowth Syndrome

Editor's comment: The comment is presented before the abstract to alert the reader to the importance of the topic.

Beckwith-Wiedeman syndrome (BWS) is characterized by intrauterine overgrowth but normal adult stature, hemihyperplasia, and an increased incidence of a variety of embryonal tumors; Simpson-Golabi-Behmel syndrome (SGBS) is associated with prenatal and postnatal overgrowth, resulting in tall adult stature (often males reach >195 cm); cleft lip/palate; polydactyly; vertebral, rib, and sternal malformations; congenital heart disease; cryptorchidism; and hypospadias. The 2 syndromes overlap as both display macroglossia, omphalocele, and an increased incidence of Wilms' tumor. BWS is associated with overexpression of paternally imprinted IGF-2 (paternal heterodisomy or isodisomy, maternal deletion of 11p15.5).

Glypicans are proteoglycans containing complex sugar molecules, such as dermatan, chondroitin, and heparin sulfate, that are anchored to the exterior of the cell membrane through glycosylphosphatidylinositol links. Four molecules currently comprise the human glypican-related integral membrane proteoglycans (GRIPS) family. Glypican-3 may modulate the growth-promoting effects of IGF-2 by acting as a coreceptor with the IGF-2 (mannose-6-phosphate) receptor (Figure 1). In the absence of glypican-3, the growth-promoting effects of IGF-2 may be unregulated. It will be interesting to learn if abnormalities in GPC3 are found in other overgrowth syndromes such as cerebral gigantism.

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The investigators have identified deletions in the gene *GPC3* for a cell-surface proteoglycan termed glypican-3 in patients with SGBS. SGBS is an X-linked (Xq26) recessive overgrowth syndrome related to, but distinct from, BWS (see above). Glypican-3 is a 580 amino acid protein whose gene contains 8 or more exons. Studying female patients with SGBS and translocations between the long arm of the X chromosome and autosome 1 and 16, the authors identified the *GPC3* gene and its deletions at the translocation breakpoint. Gene sequence was 94% homologous with a previously identified rat cell-surface proteoglycan, thus permitting characterization of the *GPC3* product as a glypican. Utilizing *GPC3* probes, the investigators detected deletions of 1 to 3 exons in 3 families with male-limited SGBS. They did not detect gross exon deletions in 3 other families, suggesting that in their affected members more subtle mutations (point mutations) in *GPC3* may be present (or that another gene defect exists with a similar phenotype to that of SGBS). *GPC3* is expressed primarily during embryologic development in mesenchymal tissues (lung, kidney, liver) and not in brain or white blood cells. With an antiserum against glypican-3, the authors demonstrated that this proteoglycan associated with IGF-2 and its binding protein(s). They suggest that SGBS may be due to defective binding of IGF-2 by glypican, thus permitting IGF-2 to exert unrestrained growth-promoting effects during embryologic development and tumor formation in later life.

Pilia G, et al. *Nature Genet* 1996;12:241-247.

Weksberg R, Squire JA, Templeton DM. *Nature Genet* 1996;12:225-227.

Second Editor's comment: Several points are made in this article. First, diagnoses of rare syndromes are not always what they seem, or are said to be, even when registered in the NIGMS repository. Investigators who use cell lines from this repository should keep this in mind when studying cells from patients whose diagnoses are difficult to make and for which specific criteria evolve over time, as commonly occurs for rare dysmorphic syndromes.

Secondly, we are reminded to keep an open mind about molecules and their biologic functions. For example, proteoglycans were originally considered boring molecules that primarily occupied space in connective tissues. Now it appears that some proteoglycans may play important roles in ligand-receptor interactions of growth factors. Another example of this phenomenon involves another proteoglycan, heparin sulfate, which appears to be required for FG ligands to bind their receptors.

Finally, the report demonstrates how several different disciplines can interact to advance the understanding of a process that may be an important regulator of growth. Indeed, this work could not have been completed without collaborations among dysmorphologists, endocrinologists, gene mappers, and molecular biologists.

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