04 ABSTRACT

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Understanding What Proteoglycans Do during Development : Lessons from the Fruitfly

profile

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Scott Selleck received his Bachelor of Arts degree in Zoology from the University of Washington, graduating *summa cum laude* in 1979. He went on to obtain both M.D. and Ph.D. degrees from Washington University Medical School in St. Louis, graduating in 1989. Upon completing his graduate studies he spent three years as a postdoctoral fellow at the Massachusetts Institute of Technology and then Brandeis University. In 1993 he joined the faculty at the University of Arizona as an Assistant Professor. He was a recipient of the Alfred P. Sloane Foundation Award for Young Investigators and the Basil O'Connor Award from the March of Dimes. In 1999 he was awarded tenure and in 2000 became the Director of the Program in Molecular Genetics at the Arizona Cancer Center. In 2002 Dr. Selleck accepted a position as Professor, Director of the Developmental Biology Center and Harrison Chair in Developmental Biology, at the University of Minnesota in Minneapolis. His research examines the molecular function of proteoglycans and glycosaminoglycans in developmental patterning and carcinogenesis.

Key words proteoglycan, development, growth factor signaling, morphogen

Drosophila melanogaster, the fruitfly, has proven to be one of the most powerful systems for gaining molecular insight into the processes of development. The recent completion of the fly and human genome projects have served to highlight the degree of functional conservation between these two organisms. For example, over 70% of genes known to be involved in human cancer are represented in *Drosophila* [1]. An increasing number of laboratories around the world are using *Drosophila* to investigate the biological functions of glycans during tissue assembly.

My laboratory has focused on the role of proteoglycans and their associated glycosaminoglycan chains in signaling during development. Our initial work determined that a *Drosophila* glypican encoded by the *division abnormally delayed(dally)* gene was required for normal patterning of cell division in the visual system[2]. Later work established that Dally affects a number of patterning decisions orchestrated by the secreted growth factors Decapentaplegic (Dpp) and Wingless (Wg), members of the TGF-β and Wnt superfamilies, respectively[3-5]. Biochemical characterization of glycosaminoglycans from *Drosophila* and structural analysis of these molecules isolated from animals bearing mutations in genes proposed to encode glycosaminoglycan biosynthesis enzymes established the high degree of conservation in the glycosaminoglycan biosynthetic pathways between *Drosophila* and vertebrates[6, 7].

More recently we have begun genetic characterization of *dally-like*, the second of two glypican-related gene in *Drosophila* [8, 9]. Our findings implicate this glypican in the control of cellular growth mediated by the insulin-like growth factor family and in patterning of the nervous system. Studies of synapse assembly and function in *Drosophila* have also shown that heparan sulfate proteoglycans play critical roles in development of the neuromuscular junction.

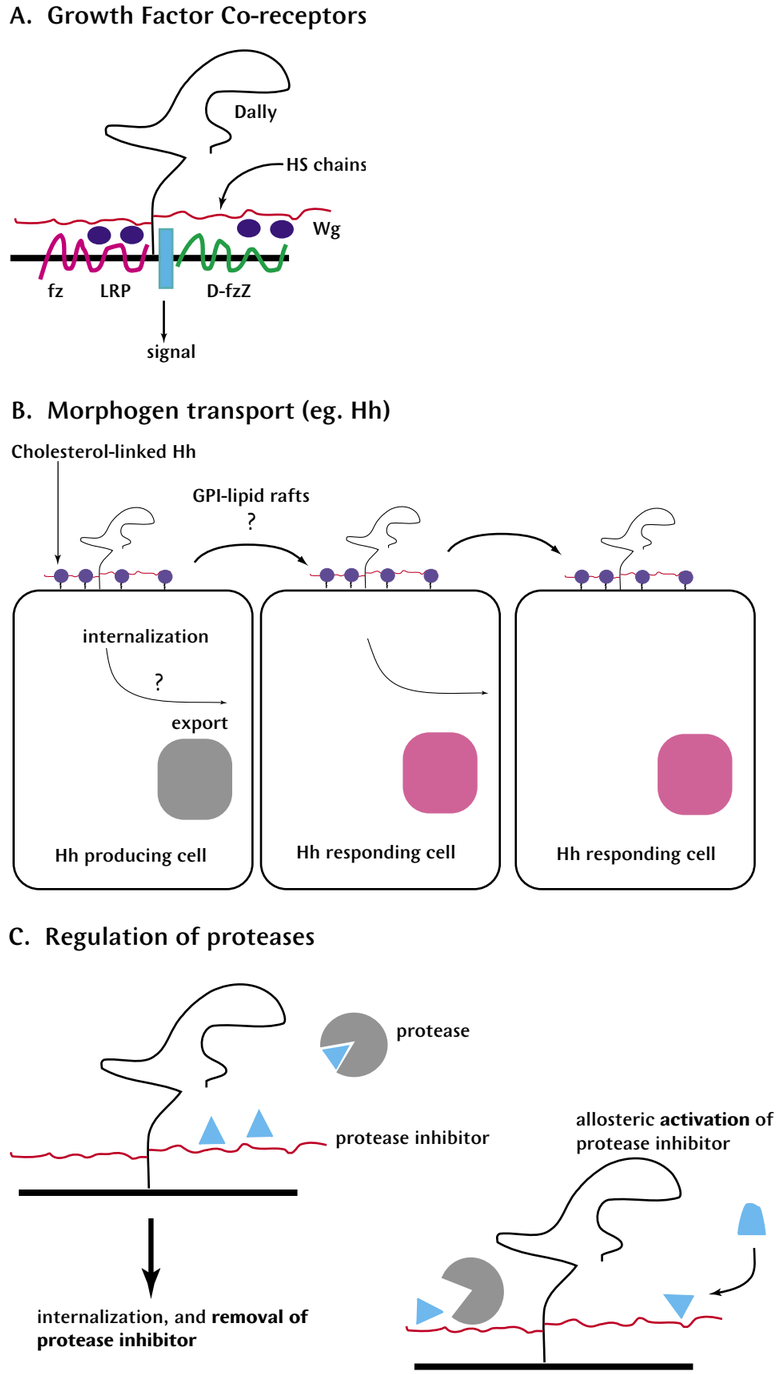

Figure 1. Models for Proteoglycan function.
(a) As an example of how a cell-surface proteoglycan might serve as a growth factor co-receptor, Dally, with its heparan sulphate chains (red), is shown bound to Wingless (Wg; blue), and affecting the assembly of a receptor complex that includes Fz, D-fzZ and LRP.
(b) tout-velu mutants disrupt heparan sulfate biosynthesis and they have been shown to be required for normal Hedgehog (Hh; green) distributions across the imaginal wing disc. Proteoglycans might affect endocytosis and the subsequent export of complexes, or 'contact-mediated' diffusion of growth factors bound to glycosylphosphatidylinositol-(GPI-) linked proteoglycans.
(c) Heparan sulfate proteoglycans have been shown to activate protease inhibitors (antithrombin III; thimble shape) and promote association of inhibitors with proteases, as well as to remove protease inhibitors from the cell surface, providing a mechanism for the activation of a protease.

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