Publications

Ryan, E., and Wang, X. (In Preparation). *Structural Interactions of Pleiotrophin with Size-Defined Heparin Fragments.*

Ryan, E., Shen, D. and Wang, X. (2016). *Structural studies reveal an important role for the pleiotrophin C-terminus in mediating interactions with chondroitin sulfate.* FEBS J, 283: 1488-1503. doi:10.1111/febs.13686
(impact factor: 4.7, citations: 9)

Deshauer, C., Morgan, A. M., **Ryan, E. O.**, Handel, T. M., Prestegard, J. H., & Wang, X. (2015). *Interactions of the Chemokine CCL5/RANTES with Medium Sized Chondroitin Sulfate Ligands*. Structure (London, England : 1993), 23(6), 1066–1077. http://doi.org/10.1016/j.str.2015.03.024

THE SCHOOL OF MOLECULAR SCIENCES

at

ARIZONA STATE UNIVERSITY

Announces the
Final Examination

Of

Eathen Ryan

For the Degree

Doctor of Philosophy

Friday, April 17, 2020
10:00 AM
Zoom: https://asu.zoom.us/j/289678175

Examining Committee

Dr. Xu Wang (Chair)
Dr. Jeffery Yarger
Dr. Wei Liu

Abstract

Structural Characterization & Glycosaminoglycan Binding of the Small Cytokine Pleiotrophin

The small mitogenic cytokine Pleiotrophin (PTN) is well-known for its roles in tissue growth, development, and repair. First isolated from neuronal tissues, much interest in this protein resides in development of the central nervous system and neuronal regeneration. Owning to its role in growth, development and its ability to promote angiogenesis and metastasis, PTN's overexpression in cancers such as glioblastoma, has become the focal point of much research. Many of the receptors through which PTN acts contain glycosaminoglycans (GAGs), through which PTN binds. Thus, understanding the atomistic detail of PTN's architecture and interaction with GAG chains is of significant importance in elucidating its functional role in growth and malignancy of biological tissues, as well as in neural development and progression of other diseases. Herein the first solution state structure of PTN was solved via nuclear magnetic resonance (NMR), with extensive characterization of its ability to bind GAG. Structurally, PTN consists of two β-sheet domains connected by a short flexible linker, and flanked by long flexible termini. Broad distribution of positively charged amino acids in the protein's sequence yields highly basic surfaces on the β-sheet domains as well as highly cationic termini. With GAG chains themselves being linear anionic polymers, all interactions between these sugars and PTN are most exclusively driven through the electrostatic interactions between them, with no discernable specificity for GAG types. Moreover, this binding event is coordinated mostly through basic patches located in the C-Terminal domain (CTD). Although the flexible C-terminus has been shown to play a significant role in receptor binding, data here also reveal an adaptability of PTN to maintain high affinity interactions through its structured domains when termini are removed. Additionally, analysis of binding information revealed for the first time the presence of a secondary GAG binding site within PTN. It is shown that PTN's CTD constitutes the major binding site, while the N-terminal domain (NTD) contains the much weaker secondary site. Finally, compilation of high-resolution data containing the atomistic detail of PTN's interaction with GAG provided the information necessary to produce the highest accuracy model to date of the PTN-GAG complex. Taken together, these findings provide means for specific targeting of this mitogenic cytokine in a wide array of biological applications.