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Dr. Afua Nyarko
Assistant Professor, Department of Biochemistry Biophysics
Oregon State University

Dynamic ensembles: novel features of multivalent IDP assemblies in Hippo signaling

Abstract:
Protein biochemistry has long been guided by the paradigm that the function of a protein is dependent on its three-dimensional structure. However, more than 30% of eukaryotic proteins do not fit this structure-function paradigm but are fully functional. These "intrinsically disordered proteins" (IDPs) or hybrids with disordered regions (IDRs) have no fixed structure and typically function via multivalent scaffolding interactions with partner proteins. The varying levels of structural flexibility make specifics of IDP/IDR binding interactions challenging to characterize. Here, we discuss our efforts using molecular biophysics approaches to characterize multivalent IDP complexes with essential roles in the regulation of cell growth. Our fundamental insight is that each regulatory complex is not a single molecular species but rather an ensemble of interconverting complexes with varying stoichiometries and/or partner protein occupancy. These findings lay important groundwork for the design of novel molecules to treat diseases such as cancer.

Bio:
Dr Afua Nyarko is an Assistant Professor in the Department of Biochemistry and Biophysics at Oregon State University. She completed her PhD studies at Ohio University, Athens, Ohio. She then moved to England for postdoctoral work in the lab of Colin Kleanthous at the University of York, followed by a second post-doctoral work in the lab of Elisar Barbar at Oregon State University. Dr Nyarko's lab uses structural biophysical approaches to investigate mechanisms of multi-protein assemblies in signaling pathways, with the ultimate goal of identifying novel strategies to selectively modulate downstream responses. She is particularly interested in the Hippo signaling pathway, a multi-component and dynamic network of protein-protein associations critical to the homeostatic balance of cell growth versus cell death. Current research efforts are directed at 1) understanding the strong link between Hippo signaling dysregulation and cancer, 2) advancing understanding of fundamental mechanisms of protein associations and how they can be modulated for therapeutic intervention, 3) the regulatory importance of multivalent intrinsically disordered proteins (IDPs) that are prevalent in Hippo signaling.