

Radhika Rawat

Senior Division Medicine & Health

Pre-Initiation Complexes of SREBP-1a and -2

The human Mediator, a ~1.2 MDa, 26-subunit protein complex, is essential in the transcription of all protein-coding genes. Activator binding triggers major structural shifts in Mediator, suggesting a means to regulate transcription: Mediator's ability to recruit different cofactors by exposing different surfaces within the complex. This structural alteration supports Mediator's facilitation of the formation of a Pre-Initiation Complex (PIC) associated with RNA Polymerase II, a group of proteins unique to each target gene that must assemble for transcription to begin. In exploring the potential gene-specificity of the PIC through differences between protein compositions of the PICs of the Sterol Regulatory Element Binding Protein (SREBP) isoforms - 1a and -2, regulators of fatty acid metabolism and cholesterol synthesis respectively, via affinity purification, we identified an enrichment of the P-TEFb and Proteasome complexes as well as others in only the SREBP-2-Mediator associated proteins, likely indicating different methods of regulation of fatty acid metabolism genes versus cholesterol synthesis genes. Upon functional validation, this dichotomy may lead to a paradigm shift in heart disease preventive care, for as the balance of fatty acids and cholesterol is central to the progression of the condition, their efficient regulation would mark a significant milestone in the development of therapeutics, suggesting alternatives to post-gene expression treatments of specific, major intermediate factors without upsetting the balance of the entire metabolic pathway.