Early protein E2 of human papillomaviruses (HPV), that are associated with cervical and anogenital cancers, regulates viral DNA replication and transactivation of procaspase-8, a component of the death-inducing signaling complex (DISC) in the extrinsic cell death pathway. This interaction bypasses the requirement of upstream adaptor proteins which are essentially required for DISC formation, thereby representing a novel adaptor-independent caspase activation pathway.

In this work, we dissected the binding interface of E2-procaspase-8 interaction using an interdisciplinary approach employing techniques such as in silico, mutational, biochemical and biophysical analyses. In vitro pull-down and coexpression studies show that E2 specifically interacts with procaspase-8 death effector domain (DED) B. We further delineated the minimal binding region in DED B using different deletion constructs. Based upon docking analyses, site-directed mutagenesis of E2 was carried out and critical residues involved in this protein-protein interaction were identified. Our results provide a molecular basis of this novel E2-procaspase-8 interaction and help in providing a model for E2-induced apoptosis in high risk HPV types. This information may be utilized in future studies to design E2 analogs so as to modulate procaspase-8 activation and hence promote apoptosis.

**Intrinsically Disordered Proteins**

**3194-Pos Board B55**

**Polypeptide Chain Collapse of Amyloidogenic Intrinsically Disordered Proteins**

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My laboratory utilizes a diverse array of biophysical tools to unravel the mechanisms of protein misfolding and aggregation leading to amyloid fibril formation [1-4]. Polypeptide chain collapse of amyloidogenic intrinsically disordered proteins (IDPs) has important consequences in protein aggregation. Using a variety of prediction and spectroscopic tools, we have first established that an archebacterial IDP namely κ-casein adopts a collapsed ‘pre-molten-globule’ like conformational ensemble under physiological condition [1]. Our results indicated a change in the mean hydrodynamic radius from ~4.6 nm to ~1.9 nm upon chain collapse.

We then took the advantage of two cysteines that are separated by 77-amino acid residues and labeled them using thiol-reactive pyrene maleimide. This dual-labeled protein demonstrated a strong excimer formation upon renaturation providing a compelling evidence of polypeptide chain collapse under physiological conditions (Figure 1). I will also discuss our recent results on biologically important amyloidogenic IDPs such as α-synuclein and disordered segment of human prion protein.