

Molecular Imaging of Protein Aggregates in Situ in Chronic Liver Diseases

Vineet Mahajan*

HPT Arts and RYK Science College, University of Pune, India

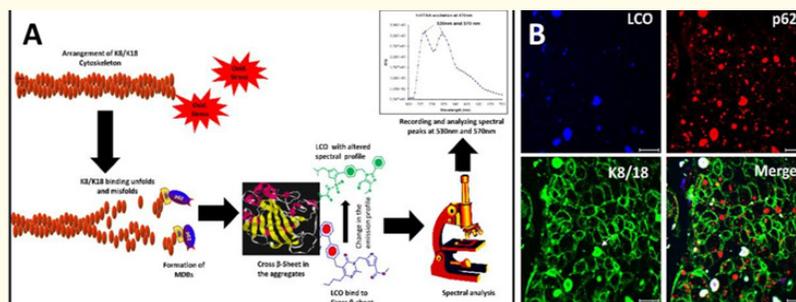
*Corresponding Author: Vineet Mahajan, Assistant Professor, HPT Arts and RYK Science College, University of Pune, Nasik, India.

Received: June 01, 2016; Published: July 11, 2016

Protein Aggregates that consist of misfolded proteins are ‘cellular hallmarks’ of several degenerative diseases. They are termed as neurofibrillary tangles and amyloid plaques in Alzheimer’s disease, Lewy bodies in Parkinson’s disease and Mallory-Denk bodies (MDBs) in steatohepatitis. MDB formation might occur due to drug intoxication and chronic cholestasis, particularly in primary biliary cirrhosis. MDBs are also observed in α 1-antitrypsin (α 1-AT) deficiency, Wilson’s disease, hepatocellular neoplasms, and idiopathic copper toxicosis. Apart from MDBs, another type of cytoplasmic hepatocellular inclusions known as intracellular hyaline bodies (IHBs) are also observed in chronic liver pathologies. While MDBs are more characteristic for alcoholic and non-alcoholic diseases (ASH/NASH), metabolic diseases, hepatocellular carcinoma (HCC) whereas IHBs have been associated with ASH or NASH induced HCC. At molecular level, MDBs consists of mainly p62, misfolded keratins (K8/18) and ubiquitin whereas IHBs contain p62 and ubiquitin but keratins are not detectable.

Despite of clinical importance of MDBs and IHBs, simple and robust method for detection of conformational variation in such aggregates in situ was not available. Spectroscopic or crystallographic methods are complex techniques with tedious procedures and often fail to precisely determine structural features of aggregates with complex protein composition. Conventional dyes such as Thioflavin T possess sterically rigid structure with lesser binding sensitivity and specificity. Moreover, they have limited emission spectrum. Therefore, new tools that help to investigate differences in the molecular structure of the components present in the various types of inclusions are crucial. These tools can help in determining new insights into the nature and genesis of protein aggregates in disease pathogenesis. Understanding structural features will be helpful for the development of better drug targeting regime.

Luminescent conjugated poly- and oligothiophenes (LCPs and LCOs) are conformation-sensitive optical probes for amyloids that consists of swiveling thiophene backbone. These luminescent ligands have also been reported to specifically bind proteins with cross β -sheet conformation and have been established as a sensitive tool for prion strain differentiation



LCOs contain rotational flexible backbone. Upon binding to the protein aggregates, this rotational freedom is restricted and generates conformation dependent emission profile as described in figure A.

Characterization of conformational changes in MDBs in situ in human and murine livers by LCO revealed many new facts. MDBs were highly positive for LCOs indicating presence of cross β -sheet conformation in all developmental stages whereas other inclusions such as

IHBs in HCC shown in figure B, lack the cross β -sheet conformation (red inclusion bodies do not get stained compared MDBs shown in white). This also indicated p62 rich IHBs are structurally different than MDBs. When compared with other inclusion bodies in other diseases ground glass inclusions in Hepatitis B or α 1-AT inclusion bodies lack the cross β -sheet conformation. Moreover, LCOs demonstrated that cross β -sheet structure can be attributed to keratins in MDBs highlighting their importance in MDB pathogenesis. Constant presence of cross β -sheet might be an effective drug target. Therefore, LCOs can be established not only as an alternative simpler, sensitive and rapid method for detection of protein aggregates but also as a biomarker due to its binding to different inclusion bodies across degenerative pathologies. Advanced imaging modalities such as positron emission tomography (PET) can gain insight into nature and genesis of protein aggregates by using radio labeled LCOs, upon availability of suitable radiopharmaceutical. Recent studies have already started to look into it.

Volume 1 Issue 2 July 2016

© All rights reserved by Vineet Mahajan.