Tauopathies are a group of neurodegenerative diseases characterized by aggregation of the Tau protein into filamentous structures. Because Alzheimer’s disease (AD) is the most common of the Tauopathies, the studies of events leading the pathological process of Tau aggregation are of great interest. In AD Tau protein aggregates abnormally as Neurofibrillary tangles (NFTs) and correlates with cognitive impairment. However, Tau in physiological conditions polymerizes poorly because it is a highly soluble protein with a poor secondary structure. This conformational change is possible because Tau contains two motifs which have a regional trend to form β-sheet structures into the microtubule-binding domain. This region is also known as the paired helical filament (PHF) core. In the present work, we express PHFcore in SH-SY5Y cells in two ways: soluble (sPHF) and with neuronal membrane localization (mPHF), to evaluate the differences between a soluble phenomenon and the membrane substrate for Tau aggregation. The results showed that expression of both constructs decreased endogenous Tau levels, probably as a defense mechanism in order to eliminate the Tau aggregates. On the other hand, when protein degradation is blocked, the Tau levels are restored and the Tau aggregates are observed with thiazine red staining and also can be extracted with sarcosyl. The filaments observed in both cases are short straight. Dependent of which protein degradation pathway is blocked, the sPHF or mPHF proteins, are processed differently. These data suggest that Tau aggregation occurs with the presence of sPHF or mPHF, but mPHF is most efficient in this process.