Nuriza Omertassova et al., J Neurol Neurophysiol 2018, Volume 9
DOI: 10.4172/2155-9562-C11-092

Parkinsonism protein DJ-1 protects cells via post-translational modification that is different from oxidation

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Human protein DJ-1 protects neurons from oxidative stress and early onset of Parkinson's disease via unknown mechanism. We have recently demonstrated that a small fraction of hexahistidine tagged human DJ-1 overexpressed in bacterial cells undergoes a transient post-translational modification on reactive cysteine (Cys106) forming a stable carboxymethyl adduct upon purification of DJ-1 from bacterial lysate. Here, we demonstrate that compared to bacterial expression, much higher proportion of DJ-1 is modified on Cys106 when the protein is overexpressed in methylotrophic yeast. Since methylotrophic yeast oxidizes methanol using molecular oxygen to generate hydrogen peroxide and formaldehyde, DJ-1 is likely to be exposed to a significant oxidative stress, suggesting that the extent of transient post-translational modification may reflect the severity of oxidant stress. To test this hypothesis we have studied whether the extent of post-translational modification of Cys106 correlates with oxidative stress. We have found that rotenone-induced oxidative stress increases the amount of post-translationally modified DJ-1 in mammalian cells. The addition of mouse brain cytosol to cell lysate with overexpressed DJ-1 resulted in a reduction of transiently modified DJ-1 suggesting the existence of a pathway that converts modified DJ-1. We conclude that an unknown metabolite reacts with Cys106 of DJ-1 to result in a relatively stable post-translational modification. This modification is different from simple oxidation to sulfinic or sulfenic acids and confers altered binding properties to DJ-1 suggesting that it may serve as a signal for sensing of oxidant stress.

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