ANALYSIS OF TOPOLOGICAL FEATURES FOR THE PRIORITIZATION OF PROTEIN SUCCINATION

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Post-translational modifications (PTMs) provide an extensible framework for regulation of protein behaviour beyond the diversity represented within the genome alone. An aberrant adduction of fumarate to certain cysteine (Cys) residues in proteins (succination) has been implicated in the pathogenesis of different disorders, such as those caused by mutations in the gene encoding fumarate hydratase on chromosome 1q42 (e.g., hereditary leiomyomatosis and renal cell cancer; Yang et al., 2014), metabolic diseases (e.g., type-2 diabetes mellitus; Frizzell et al., 2011), and possibly other conditions (Piroli et al., 2016). Moreover, by perturbing the intra/inter-protein signal transmission, succination could contribute to the variability in the response to drugs. In the last years, over 200 modified sites across more than 180 eukaryotic proteins have been identified experimentally. However, the biological role of protein succination still remains elusive. In addition, the need of methods that predict the functional impact of this type of PTM on protein behaviour has not yet been met (Miglio et al., 2016). In this study, the predictive and diagnostic value of new computational approaches, combining concepts of network theory and machine learning, has been evaluated for the prioritization of protein succination. A set of 278 Cys residues (50 modifiable and 228 non-modifiable Cys residues) found in 41 proteins was examined. The predictive value of 11 topological features was assessed with respect to the Cys reactivity. A library of 15 classification algorithms was used to analyse the computed data. The mean values of the performance parameters accuracy and area under the receiver operating characteristic curve were >0.8 (excellence prediction) for 6 algorithms, indicating that the topological features are powerful predictors of Cys reactivity toward fumarate. The diagnostic value of centrality measures (degree, betweenness and closeness) was also evaluated with respect to the impact of succination on protein behaviour. Significant differences in the rates of functional-modifiable Cys residues were found when the groups of nodes characterized by high, intermediate or low centrality in protein networks were compared, indicating that the analysis of centrality measures could lead to the identification of functional sites in proteins. In conclusion, the analysis of topological data of residue networks could have important implications for understanding protein structure and function. In particular, our findings demonstrate that it can provide helpful strategies for quantifying the likelihood of a Cys residue to be modifiable, regulatory and/or impactful on protein function.

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Piroli et al (2016). Mol Cell Proteomics. 15, 445-61.

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