Mechanism related to the onset of various genetic diseases revealed

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Researchers at the Department of Biochemistry and Molecular Biology of Universitat Autňnoma de Barcelona (UAB) have revealed the process by which proteins with a tendency to cause conformational diseases such as amyotrophic lateral sclerosis, familial amyloidotic polyneuropathy, familial amyloidotic cardiomyopathy, etc. finally end up causing them.

Researchers have carried out an analysis of their 3D structure and studied why these proteins finally become toxic although they are correctly folded, an indicator that they are functioning correctly. The answer can be found in the separation of the proteins, which under normal conditions are found in groups of two or more, caused by a genetic mutation in their composition. Researchers believe this discovery, published recently in the journal *PLoS Computational Biology*, could also be the cause of other diseases of unknown origins.

Every day cells produce thousands of new proteins which renew themselves every second and which, by obeying the orders prescribed in our genetic code, work towards the proper functioning of our body. However, these proteins occasionally suffer genetic mutations which can cause changes in their composition, thus preventing them from carrying out their functions and the activities they are assigned. In many cases this gives way to the formation of toxic macromolecular aggregates - amyloid fibrils - which block our body's protein quality control system and finally provoke cell death.

Protein aggregation and the misfolding of proteins can be linked to the

origin of many conformational diseases which can be either genetic or spontaneous. The proteins involved can either have an unstructured or lineal unfolded form such as in Alzheimer's and Parkinson's disease or Type II Diabetes, or can be globular, showing a folded 3D-structure. The former have been widely characterised by scientists and the process by which they unfold is known. The process leaves regions uncovered which are in the risk of becoming aggregated and these eventually form toxic assemblies. Globular proteins are known to be linked to hepatic, cardiac, renal and neurological disorders. However scientists do not know exactly how they manage to aggregate despite the fact that they are correctly folded within the body.

Through computational analysis, researchers Salvador Ventura and Virgínia Castillo, from the UAB Department of Biochemistry and Molecular Biology, have discovered that, in non-disease conditions, globular proteins related to conformational diseases are found associated in pairs to other proteins or in complex subunits, in a way that one protein covers the aggregation-prone region of the other and thus prevents the onset of this process. Therefore these regions remain obscured in the interior of the structure and are inoffensive to the organism as long as the two proteins are joined together. Researchers have found that genetic mutations produced in the interaction sites of the protein pair prevents their association, leaving aggregation-prone regions uncovered and favouring the formation of toxic aggregates. According to researchers, this would explain why out of two people with the same globular proteins and the same risk regions, only the one who suffers a genetic mutation would finally develop a disease.

The conclusions obtained have led researchers to contemplate the possibility that dissociation is a general mechanism, which not only affects globular proteins with a clearly defined structure, but also others which have not yet been characterised and which could be the cause of diseases of unknown origin.

As possible strategies to prevent the dissociation of proteins, the authors propose introducing genetic mutations into the proteins to strengthen their association and developing specific molecules to block the risk regions of already dissociated proteins.

The results of the study carried out by UAB researchers coincides with those obtained by researchers at Cambridge University, who also published similar data in the journal Proceedings of the National Academic of Sciences.

In the future UAB researchers are planning to expand their computational analysis to cover the whole set of human proteins with a defined 3D-structure. With this objective they seek to discover the proteins responsible for different genetic diseases of unknown origins and offer a series of new therapeutic targets for these disorders.

More information: Castillo V, Ventura S (2009). "Amyloidogenic Regions and Interaction Surfaces Overlap in Globular Proteins Related to Conformational Diseases". *PLoS Computational Biology*. Volume 5, Issue 8, August 2009.

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