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The international debate on The international debate on Posttranslational modifications of beta2-glycoprotein I alter its structural dynamics

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Beta2-glycoprotein I (beta2GPI) is a soluble blood protein (326 AA, five domains) exhibiting two main conformational states: the circular or closed conformation, where the first domain (DI) is bound to the last domain (DV) of the protein; and the linear or open conformation. In the open form, beta2GPI binds to phospholipid membranes via DV and this form is considered to play a crucial role in the autoimmune disease antiphospholipid syndrome (APS). Therefore, investigating the structural dynamics of this protein is of high interest. We investigated different post-translational modifications (PTM) of beta2GPI and studied the impact on its conformation with biophysical tools (e.g. atomic force microscopy, circular dichroism spectroscopy). Additional insights into the interaction of DI and DV were gained from molecular dynamic simulation studies. PTM 1: Lysine residue acetylation reveals a partial opening of beta2GPI dependent on the acetylation ratio used (Buchholz et al., PCCP 2018). These data indicate that lysines predominantly stabilize the closed conformation and in vivo acetylation via acetyltransferases could destabilize the closed form, leading to a facilitated opening of the structure. PTM 2: Enzymatic reduction of the C-terminal Cys288/Cys326 disulfide bond near the putative contact interface of DI and DV also initiates a conformational change of beta2GPI. Furthermore, disruption of this disulfide bond leads to loosening of a 22 AA flexible loop carrying lysine residues critical for phospholipid membrane binding. In summary, these PTM reveal a critical level of destabilization of the closed beta2GPI conformation and beta2GPI conformational change may have a large impact on APS disease.

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