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Computational Approach for Grp78–Nf-KB Binding Interactions in the Context of Neuroprotective Pathway in Brain Injuries

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Abstract : GRP78 participates in multiple functions in the cell during normal and pathological conditions, controlling calcium homeostasis, protein folding and unfolded protein response. GRP78 is located in the endoplasmic reticulum, but it can change its location under stress, hypoxic and apoptotic conditions. NF-κB represents the keystone of the inflammatory process and regulates the transcription of several genes related with apoptosis, differentiation, and cell growth. The possible relationship between GRP78-NF-κB could support and explain several mechanisms that may regulate a variety of cell functions, especially following brain injuries. Although several reports show interactions between NF-κB and heat shock proteins family members, there is a lack of information on how GRP78 may be interacting with NF-κB, and possibly regulating its downstream activation. Therefore, we assessed the computational predictions of the GRP78 (Chain A) and NF-κB complex (IkB alpha and p65) protein-protein interactions. The interaction interface of the docking model showed that the amino acids ASN 47, GLU 215, GLY 403 of GRP78 and THR 54, ASN 182 and HIS 184 of NF-κB are key residues involved in the docking. The electrostatic field between GRP78-NF-κB interfaces and molecular dynamic simulations support the possible interaction between the proteins. In conclusion, this work shed some light in the possible GRP78-NF-κB complex indicating key residues in this crosstalk, which may be used as an input for better drug design strategy targeting NF-κB downstream signaling as a new therapeutic approach following brain injuries.

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