Cyclosporine A binding to COX-2 reveals a novel signaling pathway that activates the IRE1? unfolded protein response sensor

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© 2018, The Author(s). Cyclosporine, a widely used immunosuppressant in organ transplantation and in treatment of various autoimmune diseases, activates the unfolded protein response (UPR), an ER stress coping response. In this study we discovered a new and unanticipated cyclosporine-dependent signaling pathway, with cyclosporine triggering direct activation of the UPR. COX-2 binds to and activates IRE1?, leading to IRE1? splicing of XBP1 mRNA. Molecular interaction and modeling analyses identified a novel interaction site for cyclosporine with COX-2 which caused enhancement of COX-2 enzymatic activity required for activation of the IRE1? branch of the UPR. Cyclosporine-dependent activation of COX-2 and IRE1? in mice indicated that cyclosporine-COX-2-IRE1? signaling pathway was functional in vivo. These findings identify COX-2 as a new IRE1? binding partner and regulator of the IRE1? branch of the UPR pathway, and establishes the mechanism underlying cytotoxicity associated with chroni