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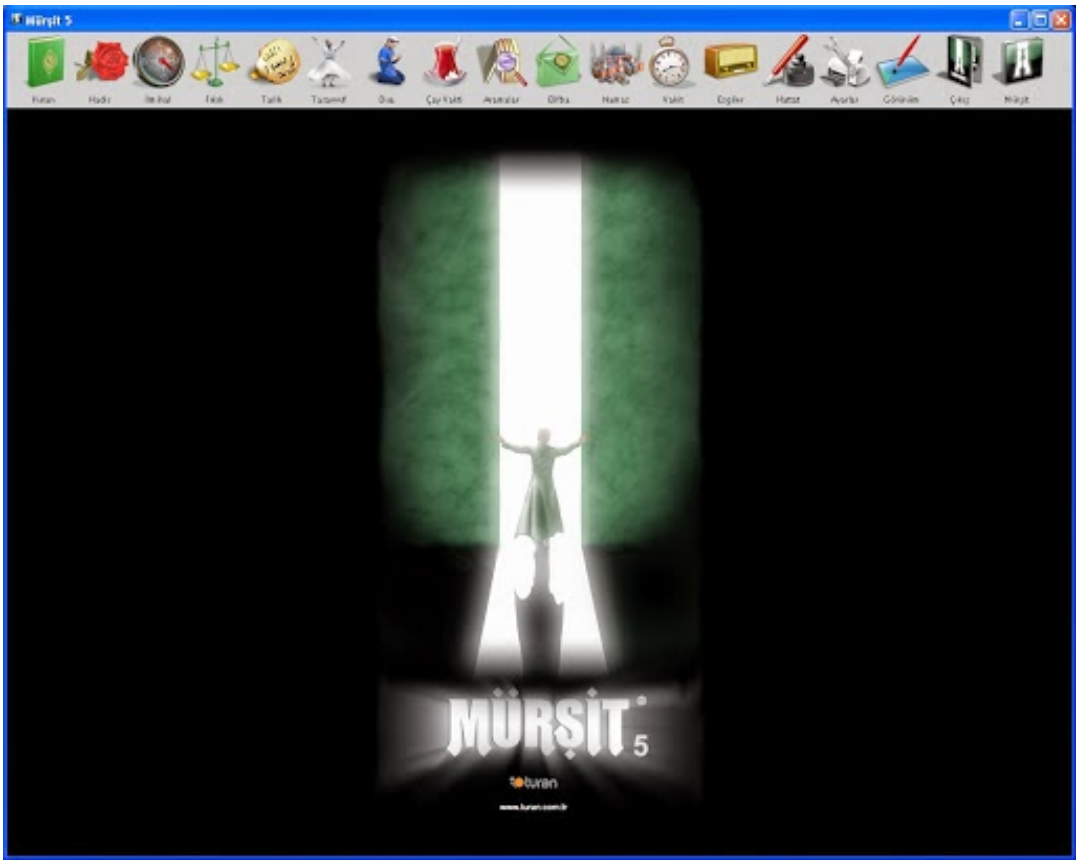

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ja4]. In addition, previous studies have shown that the catalytic activity of both Hsp90 isoforms is strongly associated with their chaperone function and client protein stabilization, which can be inhibited by small molecules [@B12], [@B13], [@B15], [@B16]. However, the molecular basis of the differential chaperone functions of Hsp90α and Hsp90β and their isoforms remains unclear. In this study, we show that protein L12 inactivates the Hsp90 chaperone activity and promotes the degradation of Hsp90 client proteins via the ubiquitin-proteasome pathway. Hsp90 clients belong to the following three classes, based on their chaperone requirements: canonical chaperone substrates, non-canonical chaperone substrates, and misfolded proteins. Non-canonical chaperones are often nucleotide exchange factors, binding partners, and cochaperones [@B21]. Thus, protein L12 may inactivate Hsp90 by facilitating the interaction between Hsp90 and its clients and inhibiting their conversion to the ATP-bound conformation, thereby preventing the translocation of Hsp90 to the cytoplasm. However, because the Hsp90-binding region of the client protein is different from that of the Hsp90-binding domain of Hsp90, protein L12 may not affect the binding of Hsp90 to the client protein. In addition, our data show that protein L12 suppresses the autophagic degradation of Hsp90 client proteins via the macroautophagy pathway. Therefore, we propose a model in which protein L12 suppresses the chaperone function of Hsp90α and Hsp90β and promotes the degradation of Hsp90 client proteins by binding to Hsp90 and inducing ubiquitination, thereby controlling the stability of Hsp90 client proteins. Our data also show that the Hsp90 chaperone functions of Hsp90α and Hsp90β are differentially regulated by their isoforms. Knockdown of Hsp90α suppresses tumor progression in cancer cells, which is opposite to the role of Hsp90β in cancer progression. This may result from the effect of Hsp90α or Hsp90β on the expression of each other. In addition, the influence of Hsp90β on the expression of other members of the Hsp90 family needs to be investigated in 82157476af