ECDO Honorary Lecture: Monitoring protein-protein interactions in autophagy, apoptosis and the cross talk between these processes.

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Apoptosis and autophagy are two distinct biological processes, each driven by a different set of protein-protein interactions. Yet there is a significant cross-talk between these two biological processes, positive or negative in its nature, that is often driven by direct physical interactions among apoptotic and autophagic proteins. In attempts to identify points of interface between these two processes we undertook two independent strategies. One is based on siRNA screens with autophagic sub-libraries searching for dual function proteins. This function-based screen resulted in the finding that the autophagic protein Atg12 displays a pro-apoptotic function in addition to its canonical autophagic functions by interacting with members of the Bcl-2 family. The second strategy is based on large scale unbiased screens for protein-protein interactions using the protein fragment complementation assay (PCA). This strategy monitors in cells the binding between pairs of proteins fused to complementary fragments of the luciferase reporter protein. To this end, we constructed a library that encompasses 63 apoptotic and autophagic proteins, and applied it in a platform that enables detection of protein-protein interactions in a high-throughput manner. By running an unbiased screen of approximately 4000 interactions between all the protein pair combinations in the library we discovered new regulatory pathways in autophagy that control DAPK2 and also identified novel 'hubs' linked to several apoptotic and autophagic proteins which will be presented in this lecture. Our work underscores the intricate interactions between these two processes suggesting that their disruption may have important pathophysiological consequences.