**The function of p63 and p73 in genetic quality control and cancer development**

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P63 and p73 are homologs of the famous tumor suppressor protein p53. Functional and structural studies, however, have revealed that both proteins have additional functions in embryonic development. In particular, p63 plays an essential role in maintaining a stem cell population in the basal layer of epithelial tissues and p63 knock out mice are born with only a very primitive skin consisting of a single cell layer and lack limbs. A second function of p63 was identified in oocytes where the protein is highly expressed and serves as a quality control factor. Using biochemical and biophysical approaches we could show that p63 is kept in a closed, inhibited and only dimeric conformation in resting oocytes. Detection of DNA damage in oocytes results in the phosphorylation of p63 which triggers a massive conformational change towards an open, active and tetrameric state. In this conformation p63 initiates apoptosis in the damaged oocytes. This mechanism can explain why women who are treated with chemo therapeutics become infertile since these drugs inflict DNA damage not only in their target cancer cells but also in oocytes.

We have investigated the closed and dimeric conformation of p63 by SAXS measurements, NMR spectroscopy as well as mutational analysis and biochemical assays and have developed a model of this inhibited state. In this model the N-terminal transactivation domain as well as a specialized C-terminal inhibitory domain play crucial roles. While both sequences are unfolded in isolation they adopt regular secondary structure elements by interacting with each other and with the central oligomerizatoin domain. In addition, we have identified the mechanism of how this closed state becomes an open, active and tetrameric conformation.

While p73 contains all domains that are necessary to adopt the closed and dimeric state and shows high sequence similarity to p63, it forms constitutive open tetramers, suggesting that the regulation of its transcriptional activity is different from the regulation of p63. Based on structural and biochemical data we have developed a model of how the activity of p73 is regulated as well.