REGULATION OF HUMAN REPRODUCTION BY p53 FAMILY MEMBERS

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ABSTRACT – The p53 protein family consists of p53, p63 and p73 transcription factors that are involved in cancer and development. Recently it was found that these proteins also regulate human reproduction. Whereas p63 is important for protection of the female germ line during meiotic arrest, p73 ensures normal mitosis in the developing blastocyst. p53 subsequently regulates implantation of the embryo through transcriptional control of leukemia inhibitory factor. Elucidating the mechanism(s) through which these factors regulate female fertility may lead to new approaches to the control of human reproduction.

EVOLUTION OF p53 FAMILY

p53, a well-known tumor suppressor and "guardian of the genome", was thought to be unique for a long time. Surprisingly, two homologs were discovered in 1997 and 1998 and named p73 and p63 (Kaghad *et al.*, 1997; Yang *et al.,* 1998). It was initially speculated that the three homologues might carry out similar functions and be capable of replacing each other. However, it is not obvious why three copies of functionally equivalent genes should be maintained through evolution.

According to phylogenetic studies, all these proteins originate from the primordial ancestor gene termed "*p63/p73*-like" (Belyi *et al.*, 2009; Belyi *et al.*, 2010). Most invertebrates have a single *p63/p73*-like gene which is expressed specifically in germ cells. The earliest organism observed during evolution expressing this ancestor gene is the sea anemone. When exposed to ultraviolet light, which happens when these organisms feed at the surface of the water, the p63/p73-like ancestor protein initiates apoptosis to protect the germ line from mistakes in genetic information (Pankow *et al.*, 2007). p63/p73-like protein localization in gametes and its function in invertebrates suggests that induction of apoptosis in the germ line upon genotoxic stress is a primordial function of the p53 family that existed already before vertebrates evolved. p63/p73-like proteins have kept their function for a billion years of evolution – in insect, molluscs, amphibians, reptiles and mammals including human (Belyi *et al.*, 2010).

In the cartilaginous fish, the ancestor *p63/p73*-like gene duplicated, and a new *p53* gene is observed along with the *p63/p73* ancestor gene (Belyi *et al.*, 2010). In bony fish there are already all three genes, *p53*, *p63*, and *p73*, and p53 has taken on its new functions ensuring the fidelity of somatic cell division (Belyi *et al.*, 2010). Within higher vertebrates, p63 and p73 have taken on new functions in development of tissues and organs, whereas p53 has become the guardian of the somatic genome and a tumor suppressor. When