The Evolution of the p53 Family of Genes: A Structural and Functional Analysis

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The human genome contains three transcription factors termed p53, p63 and p73 which are related orthologues. The function of the p53 protein is to respond to a wide variety of stresses which can disrupt the fidelity of DNA replication and cell division in somatic cells of the body. These stress signals, such as DNA damage, increase the mutation rate during DNA duplication and so an active p53 protein responds by eliminating clones of cells with mutations employing apoptosis, senescence or cell cycle arrest. In this way the p53 protein acts as a tumor suppressor preventing the mutations that can lead to cancers. The p63 and p73 proteins act in a similar fashion to protect the germ line cells in females (eggs). In addition the p63 protein plays a central role in the formation of epithelial cell layers and p73 plays a critical role in the formation of several structures in the central nervous system.

Based upon their amino acid sequences and structural considerations the oldest organisms that contain an ancestor of the p53/p63/p73 gene are the sea anemone or hydra. The present day representatives of these animals contain a p63/p73 like ancestor gene and the protein functions in germ cells of this animal to enforce the fidelity of DNA replication after exposure to ultraviolet light. Thus the structure and functions of this gene family have been preserved for over one billion years of evolution. Other invertebrates such as the worm, the fly and the clam contain a very similar ancestor gene with a similar

set of functions. The withdrawal of a food source from a worm results in the p63/p73 mediated apoptosis of the eggs so that new organisms will not be hatched into a poor environment. A similar response is thought to occur in humans. Thus this ancestor gene ensures the fidelity of the next generation of organisms.

The first time a clearly distinct new p53 gene arises is in the cartilaginous fish and in the bony fish a separation of the p63 and p73 gene occurs. After that there are very limited evolutionary changes that are found in the p63 gene and only a few changes in the p73 gene core. By contrast the p53 gene evolves rapidly and extensively obtaining the new functions of surveillance of DNA replication and cell division after stress in the somatic tissues of the body. This appears to coincide with the enhanced use of the strategy of stem cells to regenerate tissues throughout the life of the organism. During primate evolution the p63 and the p73 genes increase their sizes due to insertions into the introns of those genes.

As Caucasians and Asians evolve from their African ancestors polymorphic changes in the p53 gene occur and are rapidly selected for in these populations. This results in the further selection of alleles in genes whose products interact with and regulate the p53 protein. These polymorphisms have dramatic impacts upon the age of onset of cancers, the frequency of cancers in the elderly, the longevity of a population and even the reproductive fecundity of a population. The p53 protein is required for efficient implantation of a fertilized egg into the uterus of a female and this helps to explain the strong selection pressures upon these genes. The p53/p63 and p73 genes are not only selected by evolutionary forces but help to set the rate at which evolutionary changes can occur. For those reasons these genes have preserved a one billion year history.