MOLECULAR STUDIES ON MARINE ANIMALS: PRELIMINARY SEARCH FOR HOMOLOGS OF GENES INVOLVED IN THE PATHOGENESIS OF HUMAN DISEASE IN THE DOGFISH SHARK (SQUALUS ACANTHIAS) AND THE FINBACK WHALE (BALAENOPTERA PHYSALUS)

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It has been determined from the results of several studies that sharks naturally have a low incidence of cancer (Lee and Langer. Science 221:1187, 1983; Oikawa et al., Cancer Letters 51:181-186, 1990, Lane. J. Adv. Med 4:263-271, 1991). This may be due to a specialization such as an immune adaptation, metabolism or a contingency at a molecular level. The aim of this pilot project was to initiate molecular studies to search for homologs of mammalian oncogenes and tumor suppressor genes in the spiny dogfish shark, Squalus acanthias.

A male spiny dogfish shark liver cDNA library was constructed in Lambda Gem-2 using the Riboclone cDNA synthesis system (Promega Corporation, Madison, Wisconsin). Restriction enzyme digested fragments from the mouse retinoblastoma gene were used as molecular probes in screening for homologs using established techniques. Three clones from the cDNA library have now been isolated and sequence studies are underway. Preliminary partial sequences indicate a degree of homology with mouse retinoblastoma. Therefore the current hypothesis is that sharks may have tumor suppressor genes that are expressed, but that mutations in these controlling genes (which can lead to oncogenic processes in mammals), may either be rare or have little consequence on the factors under their control. If this is the case it is imperative that further investigations need to be initiated as such studies may pinpoint processes that could help in the understanding of the genesis of cancerous growth in mammals and humans.

The cetacean central nervous system is highly advanced but has not been used rationally in comparative study with human neurological diseases. It has been determined that apolipoprotein E 4 (ApoE 4), an isoform of apolipoprotein E (ApoE), has a functional role in the pathology of late onset Alzheimer's disease (LOAD) (Strittmatter et al., Proc.Natl. Acad. Sci. USA 90: 1977-1981, 1993). ApoE isoforms also have a role in atherosclerosis, a disease that has not been observed in whales.

Degenerate primers were designed from knowledge of the sequence and genetic structure of human ApoE. Genomic DNA was prepared from a skin sample taken from a Finback whale (Balaenoptera physalus) and used in PCR in conjunction with 2 pairs of ApoE primers. One pair of primers produced an approximately 300bp fragment which hybridized to a ^{32}P-labelled human ApoE probe. This implies a functional ApoE gene might exist in cetaceans. It is not surprising that ApoE is found in cetaceans as this high density lipoprotein is found in most human tissues where it has important roles in cholesterol and lipid transport. It would be useful to clone and sequence this whale specific ApoE, study its biochemistry and determine its role in cetacean neurological biochemistry. The molecular and biochemical studies in neurologically advanced mammals (cetaceans) evolutionarily far removed from humans may pinpoint key genes or processes that may be involved in the pathology of human diseases .

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