American Journal of
Biomedical Science & Research

www.biomedgrid.com
ISSN: 2642-1747

Mini Review

Cellular Mechanisms of Chromosomal Damage in Fish Models During the Early Steps of Carcinogenesis. Does Gender have an Effect?

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To Cite This Article: *Patrizia Guidi, Margherita Bernardeschi, Cellular Mechanisms of Chromosomal Damage in Fish Models During the Early Steps of Carcinogenesis. Does Gender have an Effect?. 2020 - 11(3). AJBSR.MS.ID.001625.* DOI: 10.34297/AJBSR.2020.11.001625.

Received: November 16, 2020; **Published:** December 16, 2020

Abstract

Since fishes are widely used as model species in understanding cellular mechanisms of many human diseases such as carcinogenesis early steps, and to test the cellular potential cellular impairment of xenobiotics such as emerging pollutants, it appears of great interest to obtain strong reliable data from fish experimental researches. In humans, the loss of chromosomal integrity, detected by the increase of micronucleus frequency, was demonstrated to be associated with early events in carcinogenesis. On the other hand, the loss of chromosomal integrity was found to be associated most frequently with sex chromosomes. We should wonder if cellular mechanisms promoting chromosomal damage in fish are influenced by the gender. This brief work tries to analyze this aspect before transferring any conclusion from fishes to humans.

Fish Model in Human Diseases

Animal models represent an indispensable tool for elucidating cellular mechanisms and pathophysiology of many human diseases such as cardiovascular and metabolic ones [1]. Mice and rats have been commonly used to translate scientific knowledge into clinical predictions, but fishes can fill some of the gaps in current animal experimentation. Many studies concerning the understanding of cellular mechanisms in a broad spectrum of human diseases have been carried out in different fish species. Research studies have been conducted not only on the widely discussed medaka (Oryzias latipes) and zebrafish (Danio rerio), but also on Antarctic fishes, cichlid fishes, blind cave fish and annual killifish, since they are models of adaptive disease phenotypes. Xiphophorus, amazon molly, damselfish, killifish are used as clinical models to understand cancer appearance/onset and cancer development mechanisms [2]. For all these reasons, particular attention deserves the use of fishes as a model species for the study of cancer.

Chromosomal Damage as End-Point

Among cellular end-points observed for the onset of cancer, micronucleus (MN) frequency deserves attention. The increase of micro-nucleated cells, which originate from whole chromosome or fragments that are not included in the main daughter nuclei during nuclear division, was demonstrated be associated with early events in carcinogenesis in human. Different events can cause the formation of MN through chromosomal rearrangements and altered gene expression or aneuploidy, effects associated with the chromosome instability phenotype often seen in cancer [3]. In dividing cells, micronucleus formation arises from chromosome breakage related to unrepaired/mis-repaired DNA lesions and chromosome malsegregation related to mitotic malfunction. Oxidative stress, exposure to clastogens or aneugens, genetic defects in cell cycle checkpoint and/or DNA repair genes, as well as deficiencies in nutrients required as co-factors in DNA metabolism and chromosome segregation machinery are involved in the induction of micronuclei [3]. In human lymphocytes sex is an important variable affecting spontaneous micronucleus formation, as reported by Fenech and co-author's [4], suggesting the possible loss of X chromosomes as an added mechanism in contributing to the micronucleus frequency increase in females. It also highlighted the importance of sex as a variable that has to be taken into

consideration when interpreting data from cross-sectional studies utilizing the cytokinesis-block micronucleus assay as a biomarker of chromosome damage. Probably autosomes and sex chromosomes are lost with the same frequency, but autosome loss would compromise cell survival. The most frequently sex chromosome lost differs respect to the sex: X chromosome in females and Y chromosome in males [5,6]. More in details, an association between aging and aneuploidy was reported in human lymphocytes [7]. At young age the frequency of X signal loss in women was similar to that observed in males but the incidence of X chromosome aneuploidy in centenarian females was appreciably higher (~22%) than that found for the Y chromosome in males [7], suggesting how aging and sex both influence major aneploigenic events and increase micronuclei frequencies in human lymphocytes.

In order to correctly interpret the results of experimental studies on cancer development cellular mechanisms which use fish as experimental model, thus feeling allowed to translate such information to humans, cellular injury resulted from clastogenic or an euploidogen events can be evaluated only after taking into account the biological parameter of gender. The aim of the present mini-review is to make an overview on micro-nucleated cell frequency in relation with sex in fish models and to recall of considering the influence of biological parameters, in particular gender and age, on understanding cellular mechanisms of diseases. In particular, the analysis of results should always include the evaluation of the variables gender and age in the statistical model used to reach a deeper understanding of the actual effect of the studied parameters like estrogenic or carcinogenic effects.

Fish Micro-nucleated Cells and Sex

Piscine MN test is enough sensitive to detect genotoxic agents and genotoxicity processes [8]. Up to now, data from literature do not report any correlation analysis with gender, taken as a statistical variable. Already in 1986, Manna and Sadhukhan [9] applied micronucleus test in gill and kidney cells of Tilapia fish, showing how the two tissue revealed different radio and chemo-sensitivity. However, the Authors did not correlate these data with the sex of specimens sacrificed, producing incomplete conclusion with respect to the experimental conditions. More recently, in a study aimed to compare the response of fish and mice to clastogenic and aneuploidogen compounds [8], MN frequency was not related with Tilapia gender, although the study suggested piscine MN assay as a genotoxicological test-system. Important variations in the frequency of micronuclei were found to be associated with both the clastogenic agent and the species investigated. To analyze the pattern of inter-specific sensitivity to micronuclei induction, a research by Koppe and co-authors [10] exposed three species of fish, Tilapia rendalli, Oreochromis niloticus and Cyprinus carpio, to four different clastogens. Authors recalled how spontaneous micronuclei induction and cell cycle kinetics of the target tissue is necessary to understand the mutagenic mechanisms at cellular level. Moreover, they showed how cell proliferation rates probably widely vary, depending on the fish species, the target tissue and environmental conditions, adding important information about the different sensitivity of species and tissues, experimental models and experimental designs, anyway, data were not analyzed taking into consideration gender as a statistical variable, likely loosing relevant informations. Whenever gender has been considered a statistical parameter to be related with micronucleated cell frequency, a statistical significant relationship was usually found. In a study aimed to detect genotoxic effects in different polluted marine environment [11], statistically significant differences were found between chromosomal alterations and gender in flounder's (Platichthys flesus) erythrocytes. The Asiatic native freshwater teleost, medaka fish (Oryzias latipes) was extensively investigated in genomic studies [12-13] and sex susceptible effects were highlighted [14]. Significant differences in micronuclei frequencies were observed in males compared with females when exposed to chlorophenolic compound (2,4,6-trichlorophenol) when no significant difference in frequencies between males and females of the untreated control group was observed [15]. Differently for what reported in the same species in gill cells treated with X-ray; fishes micro-nucleated cells frequency and body weight were found not significantly correlated, and any difference between the sexes, in terms of MN, was found [16]. The involvement of gender in modulating the mechanisms related to the onset of micronucleus seems to be influenced by tissue and/or toxicity mechanisms of the different chemical compounds.

Summary

In summary here is briefly reported the importance of statistically related results obtained on fish models with fish sex. Gender is a variable known to influence the expression of chromosomal damage in humans, thus it needs to be taken into consideration if transferring information from fish models to human diseases. We invited colleagues working on mutagenesis and carcinogenesis cellular mechanisms in fish models to include biological parameters when they analyze and comment their results, in order to reach a deeper understanding of the topic investigated.

Acknowledgement

The Authors thank Professor Giada Frenzilli for precious suggestions during the writing of the present work.

Conflict of Interest

There is no conflict of interest.

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