



Effects of alpha particles on zebrafish embryos

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ABSTRACT

Dechorionated zebrafish embryos were irradiated at 1.5 h post fertilization (hpf) to low-doses of alpha particles, viz., 1.4, 2.8, 5.6, 11.2 mGy (determined using Monte Carlo simulations). At 24 hpf, these embryos were then examined for apoptotic cells through acridine orange staining. The mean number of apoptotic cells was found to decrease significantly from controls to 1.4-mGy irradiation, and then to increase almost linearly to 2.8, 5.6 and 11.2-mGy irradiation. This trend is a typical characteristic of a hormetic effect.

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1. Introduction

Radiation hormesis describes the phenomenon that low doses of ionizing radiation have beneficial effects (Calabrese and Linda, 2003; Kaiser, 2003; Feinendegen, 2005). According to this effect, ionizing radiation at natural environmental levels may promote health by stimulating defense and repair mechanisms. Nevertheless, the radiation hormesis model does not dispute the detrimental effects associated with irradiations much higher than the natural environmental levels. The 2005 report of The Académie des Sciences-Académie nationale de Médecine (French Academy of Sciences-National Academy of Medicine) remarked that 40% of laboratory studies on cell cultures and animals have observed radiation hormesis (Dupont, 2003; Calabrese, 2004), but at the same time also cautioned that occurrence of radiation hormesis in humans was not yet well established (Aurengo et al., 2005).

The most studied ionizing radiation at natural environmental levels is the alpha particles emitted from progeny of ²²²Rn gas, exposures to which are shown to lead to lung cancers. It is well established that elevated levels of radon gas and its progeny in underground mines have posed significant lung-cancer risks for the miners. However, miner exposures were typically 30 times larger than residential exposures, so extrapolation of risk over such a substantial range of exposures remains dubious.

There have been more than twenty case-control studies of the dependence of lung-cancer risk on radon levels in homes. A meta-analysis of 17 studies suggested a linear dependence (Pavia et al., 2003). The pooled analysis of seven North American studies (Krewski et al., 2005, 2006) found agreement with the “linear, no

threshold” (LNT) model but the 95% CI included the possibility of a threshold. The pooled analysis of 13 European studies (Darby et al., 2005) produced data which also fitted the LNT model but the 95% CI excluded a threshold. Furthermore, the two poolings of Chinese data (Lubin, 2003; Lubin et al., 2004) excluded a threshold. Conversely, in the most recent case-control study, Thompson et al. (2008) found evidence supporting a hormetic dose-response for radon exposures < 150 Bq m⁻³, which deviated significantly from the LNT scenario. Thompson et al. (2008) attributed the differences in the outcomes to the design in their studies, such as locations of the radon monitors, weighting of measurements according to in-house mobility, and corrections according to changing lifestyle.

Ecological studies of the dependence lacked the individual matching of case-control studies. The studies by Cohen (1995, 1997) were by far the largest and most fully analyzed, also having been criticized and defended. Interestingly, they also found a hormetic response. However, the BEIR VI report (National Research Council, 1999) reviewed the ecologic studies and judged that they were not informative because of inherent limitations of the ecologic method.

On the cellular level, evidence is accumulating that exposures to low doses of oxidants may have a stimulatory effect on cellular processes (Macklis and Beresford, 1991; Miyachi, 2000), in contrast to cytotoxic effects of exposures to high doses. In this connection, Miyachi et al. (2003) attempted to study the effect of low doses of X-ray on zebrafish development. They found a significant decrease in time to hatching following exposures of the zebrafish embryos to 0.025-Gy X-ray irradiation during the cleavage period (1.5 h after fertilization), and also observed that the greatest decrease in this interval after exposures during the blastula period (3.5 h). On the other hand, they also noticed that this radiation-induced effect was eliminated when the dose was increased to 0.15 Gy. They concluded that exposures to low-dose

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X-rays might induce positive effects on physiological functioning (Miyachi et al., 2003).

Based on the finding of a hormetic dose-response for low-level radon exposures (Thompson et al., 2008) and the positive effects on physiological functioning of zebrafish embryos induced by low-dose X-rays (Miyachi et al., 2003), it becomes pertinent to study the radiation hormesis for low-dose alpha particles in zebrafish embryos, which forms the objective of the present work. In the present work, the zebrafish, *Danio rerio*, a small vertebrate from Southeast Asia, will be employed. It is remarked here that, in recent years, *Danio rerio* has become a preferred model for studying human disease, including carcinogenesis. The most important advantage is that the human and zebrafish genomes share considerable homology, including conservation of most DNA repair-related genes (Barbazuk et al., 2000). Rapid embryonic development is another advantage in that major organ systems become evident within 24 h post fertilization (hpf).

2. Materials and methods

2.1. Dechoriation of zebrafish embryos

A number of previous research works have been carried out using the zebrafish embryo as an *in vivo* model to study the DNA damage response to ionizing radiation. However, energetic photons (X-rays and gamma rays) were normally used (e.g., Bladen et al., 2005; McAleer et al., 2005, 2006; Daroczi et al., 2006; Geiger et al., 2006). As mentioned in the introduction, the objective of the present work was to study the radiation hormesis for low-dose alpha particles in zebrafish embryos. Recently, we described an experimental setup for studying the effects of alpha particles on zebrafish embryos (Yum et al., 2007). One of the extra steps in dealing with the zebrafish embryos (when compared to those in experiments using X-rays and gamma rays) was the dechoriation of zebrafish embryos before alpha-particle irradiation, since the chorions would absorb a significant fraction of the alpha-particle energies. In the present experiments, the embryos were placed in a petri-dish lined with a layer of agarose, where their chorions were removed by hand with forceps.

2.2. Alpha-particle irradiation of zebrafish embryos

About 40 dechoriated embryos were prepared for alpha-particle irradiation each time. They were first transferred into a

custom-made PADC-film based holder as shown in Fig. 1 (see Chan et al., 2006). Polyallyldiglycol carbonate (PADC) films were used as the substrate because they were biocompatible (e.g., Li et al., 2006) and their thickness could be controlled precisely through chemical etching to control the residual alpha-particle energy incident onto the dechoriated embryos (Yum et al., 2007). For alpha-particle irradiation of zebrafish embryos, it is only feasible to quantify the alpha energies incident on the embryos if the alpha particles pass through the substrate to strike the embryo cells (Fig. 2), because there is always a fluid layer with variable thickness above the embryos. PADC films are one of the most commonly used solid-state nuclear track detectors, on which a recent review on SSNTDs has been given by Nikezic and Yu (2004). In the present work, PADC films with a thickness of 16 μm were prepared from commercially available PADC films with a thickness of 100 μm (from Page Mouldings (Pershore) Limited, Worcestershire) by chemical etching in NaOH/Ethanol (Chan et al., 2007), which were then glued by an epoxy (Araldite[®] Rapid, England) to the bottom of a custom-made holder.

In the present work, alpha-particle irradiation of the dechoriated zebrafish embryos were made with a planar ²⁴¹Am source (with an alpha-particle energy of 5.49 MeV under vacuum and an activity of 4.259 kBq (0.1151 μCi) from the side of the PADC film at 1.5 hpf. At this developmental stage, the cells have not assumed differentiated cell fates. This time point (1.5 hpf) is also within the cleavage period of embryogenesis (0.7–2.2 h) (Kimmel and Law, 1985; Kimmel et al., 1995). Walker and Streisinger (1983) found that embryos older than 3 h were considerably more resistant to γ -rays, which suggested a possible repair mechanism after the cleavage stages.

Considering the physical size of the cells in the embryos and the large number of alpha particles involved, the absorbed dose received by the embryos can be surrogated by the irradiation

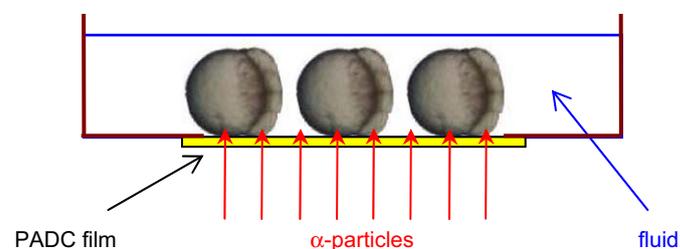


Fig. 2. The irradiation of the zebrafish embryos through the PADC-film based holder.

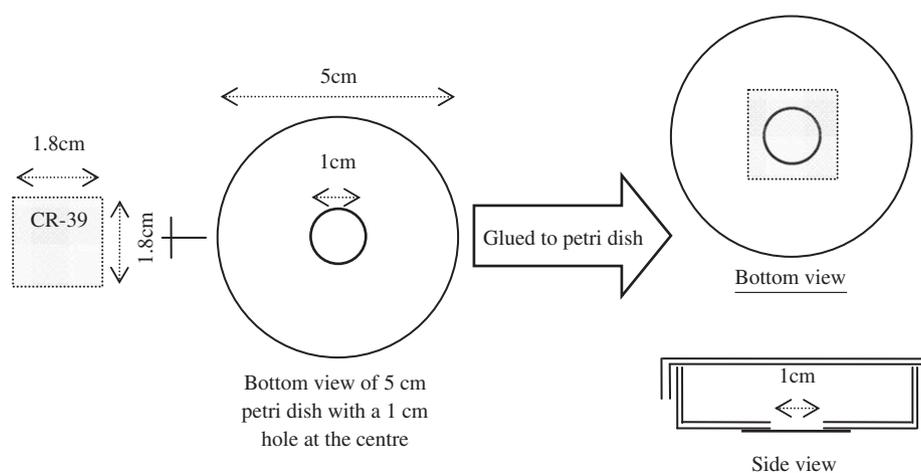


Fig. 1. Preparation of a custom-made PADC-film based holder by gluing a thin PADC film onto the bottom of a petri dish with 5 cm diameter and with a 1 cm hole drilled at the center of the bottom (Chan et al., 2006).

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