Toxicology and Applied Pharmacology 331 (2017) 135–141

Contents lists available at ScienceDirect

Toxicology and Applied Pharmacology

journal homepage: www.elsevier.com/locate/taap

Radiation exposure from depleted uranium: The radiation bystander effect

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ARTICLE INFO

Article history:
Received 25 February 2017
Revised 22 May 2017
Accepted 7 June 2017
Available online 9 June 2017

ABSTRACT

Depleted uranium (DU) is a radioactive heavy metal used primarily in military applications. Published data from our laboratory have demonstrated that DU exposure *in vitro* to immortalized human osteoblast cells (HOS) is both neoplastically transforming and genotoxic. *In vivo* studies have also demonstrated that DU is leukemogenic and genotoxic. DU possesses both a radiological (alpha particle) and chemical (metal) component but is generally considered a chemical biohazard. Studies have shown that alpha particle radiation does play a role in DU's toxic effects. Evidence has accumulated that non-irradiated cells in the vicinity of irradiated cells can have a response to ionization events. The purpose of this study was to determine if these "bystander effects" play a role in DU's toxic and neoplastic effects using HOS cells. We investigated the bystander responses between DU-exposed cells and non-exposed cells by co-culturing the two equal populations. Decreased cell survival and increased neoplastic transformation were observed in the non-DU exposed cells following 4 or 24 h co-culture. In contrast Ni (II)- or Cr(VI)- exposed cells were unable to alter those biological effects in non-Ni(II) or non-Cr(VI) exposed co-cultured cells. Transfer experiments using medium from the DU-exposed and non-exposed co-cultured cells was able to cause adverse biological responses in cells; these results demonstrated that a factor (s) is secreted into the co-culture medium which is involved in this DU-associated bystander effect. This novel effect of DU exposure could have implications for radiation risk and for health risk assessment associated with DU exposure.

1. Introduction

Depleted uranium (DU) is a dense heavy metal and an alpha particle emitter used in military applications. It has been used in military conflicts in Iraq, Bosnia, Kosovo and the technology has been established for future use by to multiple nations. Exposure can occur *via* wounding, ingestion, or inhalation. During the 1991 Gulf War and the recent Iraq War, several soldiers were wounded during friendly fire accidents and now have chronic internal exposure to DU; additionally the extent of DU inhalation by soldiers and civilians during previous military operations is difficult to verify.

Recent studies have investigated the potential health effects of this unique heavy metal which is also a radioactive heavy metal [Miller, 2007; McClain and Miller, 2006]. These *in vitro* investigations, reviewed in Fig. 1, have not only demonstrated the neoplastic transforming ability, the mutagenicity, and the genotoxicity of DU, but also that DU exposure can induce genomic instability in a human cell model [Miller, 2007a; McClain and Miller, 2006]. Furthermore some results demonstrated that alpha particle radiation is responsible for some of the cellular damage induced by DU [Miller et al., 2002a; Miller et al., 2007] while others suggested that chemical damage is responsible for DU-effects (Miller et al., 2002b; Stearns et al., 2005). *In vivo* studies of DU implants in rodent models, reviewed in Fig. 2, have demonstrated the carcinogenicity (Hahn et al., 2002), neurotoxicity (Pellmar et al., 1999), and leukemogenic effect (Miller, 2005; Miller et al., 2009) of chronic long-term internal exposure to embedded DU. Renal dysfunction following long-term chronic exposure has been observed as well (Zhu et al., 2009). Inhalation studies *in vivo* have also demonstrated that inhaled DU is genotoxic (Monleau et al., 2006), inhibits vitamin metabolism (Tissandie et al., 2006), accumulates in brain (Houpert et al., 2007), and adversely affects rodent behavior (Monleau et al., 2005).

DU has a low specific activity in comparison to natural uranium, and was not considered to be a significant external radiological hazard prior to recent uses. However, studies have demonstrated that DU exposure intracellularly can cause radiation effects *in vitro* (Miller et al., 2001;

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http://dx.doi.org/10.1016/j.taap.2017.06.004
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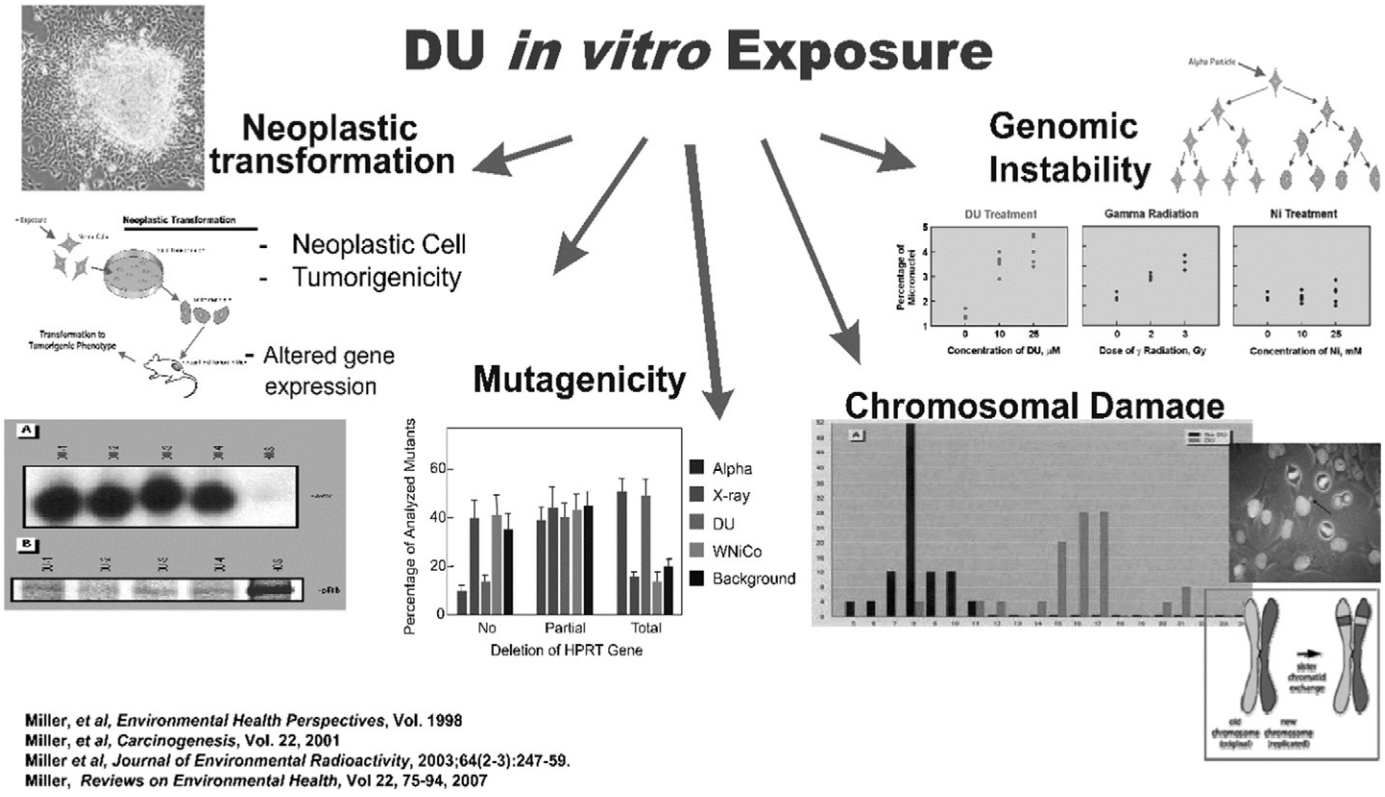

Fig. 1. Review of depleted uranium *in vitro* studies. Counterclockwise from top left: DU-induced Neoplastic Transformation; DU-induced mutagenicity; DU-induced chromosomal damage; DU-induced genomic instability *in vitro*. References for each study are listed in the figure.

Miller et al., 2007). Cytogenetic studies showed that DU exposure could induce chromosomal dicentrics which are considered a radiation-specific chromosomal damage (Miller et al., 2001). A second approach was used to further evaluate DU radiation-specific damage. The induction of mutagenic damage in V79 cells was examined using three uranyl nitrate compounds each containing a different isotope of uranium to determine if radiation plays a role in the induction of that damage. Mutagenicity assessments at the hypoxanthine (guanine) phosphoribo syltransferase *(hprt)* locus demonstrated that equal uranium concentrations with increasing specific activities could induce a specific activity-

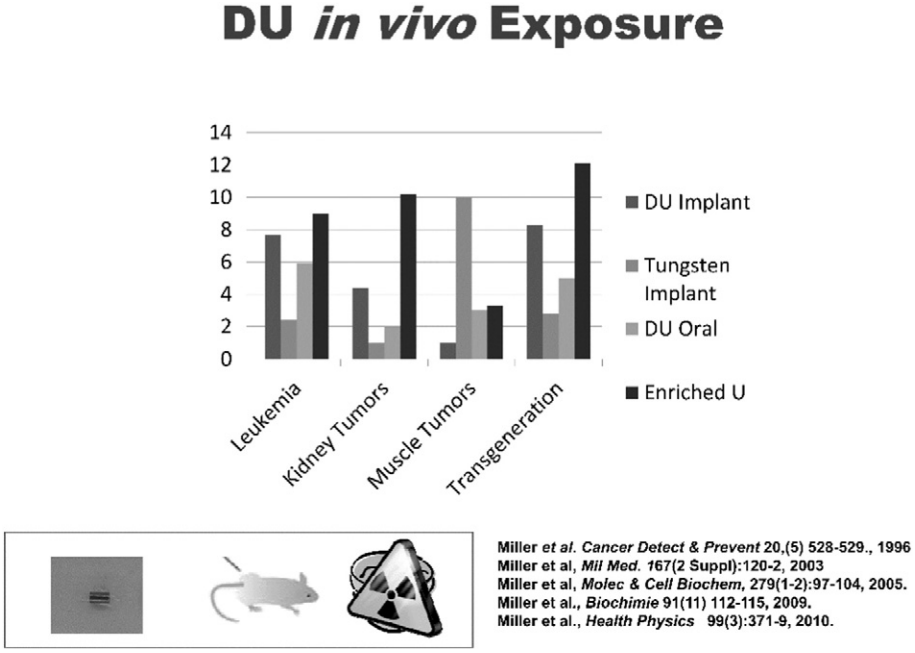

Fig. 2. Review of depleted uranium *in vivo* studies. The bar graph illustrates several studies done to evaluate DU implants in comparison to tungsten implants, DU oral administration, or Enriched 235U oral exposure in mice. Endpoints assessed included leukemia, kidney tumors, muscle tumors, and transgenerational effects. The bottom panel illustrates the implant model system. References for each study are listed in the figure.