Toxicology Letters 334 (2020) 4–13

Contents lists available at ScienceDirect

Toxicology Letters

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

Repeated radon exposure induced lung injury and epithelial–mesenchymal transition through the PI3K/AKT/mTOR pathway in human bronchial epithelial cells and mice

Huiqin Chen[a,b,1], Na Chen[a,b,1], Fengsheng Li[c,1], Liang Sun[a,b,1], Jicong Du[d], Yuanyuan Chen[d], Fei Cheng[c], Yanqing Li[a,b], Siqi Tian[a,b], Qisheng Jiang[c], Fengmei Cui[a,b,*], Yu Tu[a,b,*]

[a] State Key Laboratory of Radiation Medicine and Protection, School of Radiation Medicine and Protection, Soochow University, Suzhou, 215123, China
[b] Collaborative Innovation Center of Radiation Medicine of Jiangsu Higher Education Institutions, Suzhou, 215123, China
[c] PLA Rocket Characteristic Medical Center, Beijing, 100088, China
[d] Department of Radiation Medicine, Faculty of Naval Medicine, Second Military Medical University, Shanghai, 200433, China

ARTICLE INFO

Keywords:
EMT
Radon exposure
PI3K/AKT/mTOR
The epithelial cells

ABSTRACT

Radon exposure is the most frequent cause of lung cancer in non-smokers. The high linear energy transfer alpha-particles from radon decay cause the accumulation of multiple genetic changes and lead to cancer development. Epithelial–mesenchymal transition (EMT) plays an important role in oncogenesis. However, the mechanisms underlying chronic radon exposure-induced EMT attributed to carcinogenesis are not understood. This study aimed to explore the EMT and potential molecular mechanisms induced by repeated radon exposure. The EMT model of 16HBE and BEAS-2B cells was established with radon exposure (20000 Bq/m^3, 20 min each time every 3 days). We found repeated radon exposure facilitated epithelial cell migration, proliferation, reduced cell adhesion and ability to undergo EMT through a decrease in epithelial markers and an increase in mesenchymal markers. Radon regulated the expression of matrix metalloproteinase 2 (MMP2) and tissue inhibitors of metalloproteinase 2 (TIMP2) to disrupt the balance of MMP2/TIMP2. In vivo, BALB/c mice were exposed to 10^5 Bq/m^3 radon gas for cumulative doses of 60 and 120 Working Level Months (WLM). Radon inhalation caused lung damage and fibrosis in mice, which was aggravated with the increase of exposure dose. EMT-like transformation also occurred in lung tissues of radon-exposure mice. Moreover, radon radiation increased p-PI3K, p-AKT and p-mTOR in cells and mice. Radon reduced the GSK-3β level and elevated the active β-catenin in 16HBE cells. The m-TOR and AKT inhibitors attenuated radon exposure-induced EMT by regulation related biomarkers. These data demonstrated that radon exposure induced EMT through the PI3K/AKT/mTOR pathway in epithelial cells and lung tissue.

1. Introduction

Radon is a ubiquitous, radioactive gas deriving from the decay of uranium and is considered a human carcinogen by the International Agency for Research on Cancer (IARC) (Cancer, 1988; Loomis et al., 2014). Radon and its progeny deposited in bronchial epithelial cells generates high energy alpha decay (α-decay) particles, which damage cell nuclei directly or through the generation of free radicals (Darby et al., 2005; Samet et al., 2009). Long-term radon exposure can cause oxidative stress, inflammatory response and result in chronic lung diseases including pulmonary fibrosis and lung cancer. Radon is the second leading cause of lung cancer behind tobacco smoke, and approximately 10–30 % of lung cancer deaths in non-smokers are attributable to radon radiation (Casal-Mourino et al., 2019; Lorenzo-González et al., 2019; Sun et al., 2007; Torre et al., 2015).

In the early stages of radiation carcinogenesis, several biological changes occur, such as cell cycle arrest, DNA damage, apoptosis, and cell senescence, and the epithelial–mesenchymal transition (EMT) is an important indicator of malignant change. EMT is the biological process by which epithelial cells are transformed into motile mesenchymal cells and is characterized by increase cell motility, disruption of cell–cell junctions, degradation of the underlying basement membrane,

* Correspondence authors at: State Key Laboratory of Radiation Medicine and Protection, School of Radiation Medicine and Protection, Soochow University, Suzhou, 215123, China.
E-mail addresses: cuifengmei@suda.edu.cn (F. Cui), tuyu@suda.edu.cn (Y. Tu).
[1] These authors have contributed equally to this work.

https://doi.org/10.1016/j.toxlet.2020.09.008
Received 21 May 2020; Received in revised form 9 September 2020; Accepted 12 September 2020
Available online 16 September 2020
0378-4274/