MRI study of the changes of perfusion and fat content in radiation-induced bone marrow injury in rats

kejun wang[1], Yunfei Zha[1], and Hao Lei[2]

[1]*Department Of Radiology, Renmin Hospital Of Wuhan University, Wuhan, Hubei, China,* [2]*Wuhan Institute Of Physics and Mathematics,Chinese Academy of Sciences, Wuhan, Hubei, China*

Introduction: Ionizing radiation damages hematopoietic stem cells and alters the capacity of bone marrow stromal elements to support and/or maintain hematopoiesis[1]，and consequently damages the hematopoietic microenvironment. In addition, bone marrow fat content and fatty acid (FA) compositions are also altered after irradiation. Dynamic contrast-enhanced MRI (DCE-MRI) is a non-invasive approach to measure perfusion process and has been widely employed in studies of bone marrow perfusion[2]. The significant changes of metabolites found in high-resolution MAS ^{1}H NMR spectroscopy in the intact bones after whole-body gamma radiation suggested that increased bone marrow fat content were the important cause of bone marrow cells necrosis[3]. The purpose of this study was to investigate whether adipocytes influence bone marrow microcirculation based on quantitative perfusion parameters of DCE-MRI and ex vivo high-resolution MAS ^{1}H NMR spectroscopy.

Methods: Thirty-six SD rats were randomly divided into irradiation group and normal control group.The irradiation group received 6.0Gy of whole body high-energy x-ray, and perfusion imaging using DCE-MRI were performed at different times before and after the irradiation. The following quantitative parameters were measured: the volume transfer constant (K^{trans}), the efflux rate constant (k_{ep}), blood plasma volume fraction (v_p) and extracellular extravascular volume fraction(v_e). Rats were then sacrificed and the bone marrow from each rat femur frozen in liquid N2 for high-resolution MAS ^{1}H NMR spectroscopy analysis. Meanwhile, the left rat femur was prepared for determination of bone marrow fat content and microvessel density (MVD) by histopathologic examination.

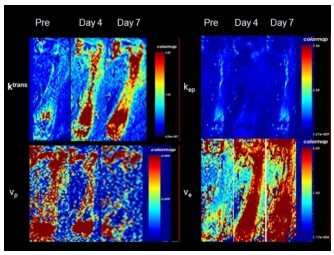

Fig.1 The irradiation group's bone marrow parameter maps of K^{trans}, v_p, k_{ep} and v_e

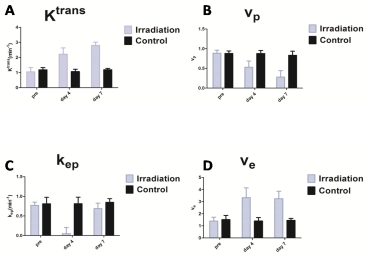

Fig.2 Histogram shows the changes of K^{trans}, v_p, k_{ep} and v_e at different time before and after the irradiation

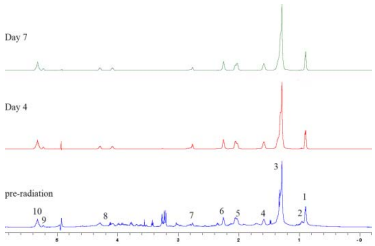

Fig. 4 ^{1}H HRMAS NMRS of ex vivo bone marrow at different time before and after the irradiation

Results: The irradiation group has statistically significant differences in K^{trans}, v_p, k_{ep} and v_e values at different time points before and after the irradiation (Fig.1). Fig. 2 shows the K^{trans} Values gradually reached a peak on the 7th day after irradiation(A), and v_p Values gradually decreased(B). The k_{ep} values decreased on the 4th day after irradiation, but increased on the 7th day compared with the 4th day(C). Although the v_e Values increased on the 4th day, there is no significant difference in v_e between the 7th day and the 4th day（P=0.249）(D). Meanwhile, adipocytes gradually reached a peak on the 7th day after irradiation(Fig. 3). The bone marrow measured fat content by histopathologic examination at different time showed correlation with K^{trans}(r= 0.7393, P<0.01) and v_p(r=-0.5841, P<0.05). The bone marrow microvessel density (MVD) showed positive correlation with v_p（r=0.6451, P<0.05）. Bone marrow fatty acid (FA) composition significantly changed at different time points after the irradiation(Fig.4). The proportion of (n−6) PUFA gradually reached a peak on the 7th day, the proportion of (n−3)PUFA gradually decreased and the proportion of saturated FA gradually increased.

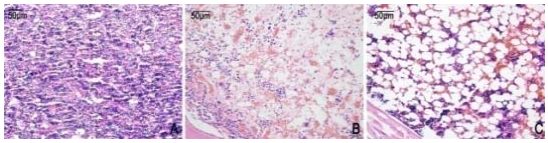

Fig.3 Histology of rat femurs, illustrating bone marrow hematopoietic cell depletion and white adipose Cells increase. A: Nonirradiated control; B: 4 days after radiation; C: 7 days after radiation

Discussion: The volume transfer constant K^{trans} gradually reached a peak on the 7th day after irradiation, whereas the v_p Values gradually decreased**.** Meanwhile, the bone marrow fat content gradually increased, which indicates that adipocytes accumulation result in the oppression of bone marrow sinusoids. This may be an important cause of the decreases of MVD and v_p. MVD shows positive correlation with v_p, indicating that vp can reflect the average density and is sensitive to perfused vessels.The proportion of (n−6) PUFA promoting vascular inflammation gradually increased, It indicates that the changes of bone marrow fatty acid(FA) composition after the irradiation may be the important cause of the injury of bone marrow microcirculation.

Conclusion: Bone marrow microcirculation perfusion and vascular permeability correlate with fat content at early stage after irradiation. There might be a pathophysiology mechanism based on fat- vascular permeability in the injury of bone marrow microcirculation.

References: 1.Cao X et al, Proc Natl Acad Sci U S A, 108(4):1609-1614(2011) ; 2. J.F. Griffith et al, Radiology, vol. 241, pp. 831-838(2006) ; 3. Zhang, Q et al,Radiat Res 172(5): 607-16(2009).