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NF-KB ACTIVATION AFTER HEAVY ION EXPOSURE: INCREASING THE SENSITIVITY OF THE REPORTER SYSTEM

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Biological effects of ionizing radiation are strongly influenced by the radiation quality. The biological effectiveness of accelerated heavy ions (which constitute the biologically most important radiation type in space) with medium to high linear energy transfer (LET), for affecting DNA damage response pathways as a gateway to cell death or survival, is of major concern for space missions. The transcription factor Nuclear Factor κB (NF-κB) can be activated during the DNA damage response. In order to determine NF-κB activation after exposure to different radiation qualities, a reporter system was constructed, in which the destabilized variant of a reporter gene (DD-tdTomato) is controlled by a synthetic promoter containing four κB binding sites for NF-κB. The current study aims to analyze NF-κB activation after exposure to space-relevant radiation qualities including ^{16}O (95 MeV/n, LET 51 keV/mum), ^{48}Ti (1000 MeV/n, LET 108 keV/mum), ^{36}Ar (95 MeV/n, LET 272 keV/mum) and ^{12}C (95 MeV/n, LET 73 keV/mum) ions by means of the HEK-pNFκB-DD-tdTomato-C8 reporter cell line. The fluorescent protein DD-tdTomato encompasses the ProteoTuner system: DD-tdTomato is rapidly degraded in human cells, but in the presence of the synthetic molecule Shield-1, the fluorescent protein is stabilized and a stronger fluorescent signal is achieved. The fluence and dose of heavy ions and the number of hits per cell nucleus that double the NF-κB-dependent DD-tdTomato expression were investigated in absence and presence of Shield-1. In absence of Shield-1, 44 hits of ^{16}O ions and 12 hits of ^{48}Ti per cell nucleus were required to double the NF-κB dependent DD-tdTomato expression whereas only 3 hits of ^{36}Ar were sufficient. In presence of Shield-1, even single particle hit of ^{36}Ar with LET 272 keV/mum doubled the NF-κB-dependent DD-

tdTomato expression. In the presence of Shield-1, the fluorescent protein DD-tdTomato was accumulated inside the cell and the detection limit for activation of NF-κB-binding site containing promoter activity after ^{36}Ar ion exposure was lowered. In conclusion, stabilization of the reporter protein can increase the sensitivity for NF-κB activation detection by a factor of three and the effect of single particle hits was detected. With this sensitive HEK-pNFκB-DD-tdTomato-C8 reporter system, agents counteracting heavy ion induced NF-κB activation can be screened at low cost.