Smad7 foci are present in micronuclei induced by heavy particle radiation

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DNA damage and reactive oxygen species (ROS) generated by ionizing radiation (IR) activate DNA damage response and cytokine signaling pathways, including double strand breaks (DSB) repair and transforming growth factor beta (TGFβ)/Smad signaling pathway. TGFβ is a cytokine regulating multiple cellular processes, through its downstream Smad proteins. Proteins assembled at DSB induced by IR can be visualized and referred as IR-induced foci (IRIF), including γH2AX, 53BP1, ATM and ATF2. Unrepaired DSBs are thought to be one origin of micronuclei (MN), an indicator of genotoxic stress and chromosomal instability. Several studies have detected γH2AX in IR-induced MN, indicating the presence of DSB in MN. Previously we have reported that Smad7 and phosphor-Smad2 (pSmad2) co-localized with DSB repair proteins following high linear energy transition (LET) particle radiation. Here we studied the status of Smad7 and pSmad2 in MN post high LET radiation in human normal cells and cancerous cells. We observed γH2AX foci in IR induced MN, where 53BP1 and ATF2 foci were absent. Interestingly, Smad7 foci, but not pSmad2, were detectable in spontaneous as well as IR-induced MN. We compared the effect of different particle track structures on the yield of MN using 5.3MeV/u boron (B) and 600MeV/u iron (Fe) particles of similar LET, 205 keV/μm and 180keV/μm, respectively, in human fibroblasts. Strikingly, the frequency of MN induced by B was much lower than that by Fe ions, albeit the proportion of Smad7-positive MN to Smad7-negative MN remained constant. A higher frequency of spontaneous MN was found in human prostate cancer cells (PC3, p53null) compared to normal epithelial cells and fibroblasts. 24h after 1Gy of Fe ions exposure, the yield of MN increased, and the majority (>70%) of MN were both γH2AX and Smad7 positive. Thus our data suggest a unique role of Smad7 in IR induced MN which may associate with genomic instability and serve as a biomarker of tumor cells.