Effects of low fluence HZE ions on 3-dimensional skin tissue.

Sally A. Amundson and Alexandre Mezentsev
Columbia University Medical Center, Center for Radiological Research, New York, NY 10032

We have used the MatTek EPI-200 3-dimensional human tissue model in studies of alpha-particle and low LET proton triggered bystander effects. We now demonstrate bystander responses in these tissues following very low fluence exposure to high LET iron (300MeV/n) ions delivered at Brookhaven National Laboratory. These experiments used specialized holders designed to allow registration of the 3-D tissues directly on top of customized pieces of L115 track-etch plastic. The tissue-and-track-etch stacks were exposed together to very low fluence iron ions (300 MeV/n), and the location of tracks and their predicted penumbra were determined from the track-etch data. The number of tracks observed in the in-beam samples agreed well with the predicted number, whereas tracks were not seen in out-of-beam controls. Superimposition of the tracks and predicted penumbra onto exposed or control tissue sections has allowed cytometric measurement of tissue changes and scoring of apoptosis in bystander tissue as a function of distance from the nearest track. The results from the low-fluence exposed tissues are compared with the out-of-beam control tissues to distinguish between true bystander effects and possible contributions of radiation resulting from activation of air or objects in the beam line, although such “stray” radiation was not detected during the experiment.

We noted a significant increase in cornification in the irradiated tissues, both within the track / penumbra area, and in the bystander areas of the tissues. Increased cornification appeared to be a far-reaching response, and resulted in an overall increase in the thickness of the cornified layer across the entire tissue, when exposed to as few as 100 iron particle tracks per square centimeter of tissue. The cornified layer was nearly twice as thick in the area within 1 mm of a particle track as it was in the same area of a non-exposed control tissue. Increased apoptosis was also detected in the bystander area around tracks. While this response showed more variability from track to track than the cornification response, perhaps due in part to differences in the timing of apoptosis, the averaged response showed significant increases in apoptosis within 400 microns of all tracks scored. Some individual tracks demonstrated extremely strong apoptotic staining that was clearly not correlated with the fall-off of energy deposition within the penumbra. We conclude that even very low fluence exposure to HZE particles is likely to produce biological effects in a much greater volume of tissue than that which directly experiences an ionization.

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