Inhibition of human mesothelioma progression in a mouse xenograft model by Micro-fragmented fat (MFAT)

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OBJECTIVE: Malignant Pleural Mesothelioma (MPM) is a tumor related to asbestos exposure with no effective therapy and poor prognosis. Our previous studies demonstrated an *in vitro* and *in vivo* inhibitory effect of adipose tissue-derived Mesenchymal Stromal Cells (MSCs) or their derivates (conditioned media, cellular lysates) on MPM. The purpose of this study was to verify whether fat tissue (FAT), a natural container of MSCs, after micro-fragmentation (MFAT) was able to exert a similar inhibitory action on the growth of the human MPM cell line (MSTO-211H) xeno-transplanted in immunodeficient mice.

MATERIALS and METHODS: MFAT was prepared according to standardized methods using Lipogems device. MSCs were obtained by enzymatic digestion of MFAT. The *in vitro* effect of MFAT on MSTO-211H cell proliferation was analyzed using transwell inserts and measuring the absorbance by a crystal violet assay. PBS were used as negative controls.

For *in vivo* experiments, Balb/c-Nude female mice were subcutaneously injected with 10^6 MSTO-211H cells suspended in Matrigel/PBS. Mice were randomized in 4 groups: control, paclitaxel (PTX), MSCs and MFAT. After a week from injection (time 0), vehicle alone (control group) or PTX (20mg/kg) were administered intraperitoneally (IP) and MSCs ($5x10^5$) or MFAT (200µl) were subcutaneously injected close to the tumor. At days 0, 7 and 14, the size of tumor nodules was measured and at day 20 nodules were collected. Morphometric evaluation of xenograft composition was performed on Masson's trichrome-stained sections.

RESULTS: The *in vitro* exposure of MSTO-211H cells to MFAT produced a dose-dependent inhibition of cell proliferation. In the *in vivo* study the measures of volume of growing tumor mass indicated that the *in situ* treatment with MFAT produced an important inhibition similar to those obtained in mice treated with the anticancer drug PTX. A trend of inhibition, but not significant, was also observed in mice treated with free MFAT derived MSCs. The morphometric analysis of the tumor xenograft did not show significant differences among groups.

CONCLUSIONS: Our results show that MFAT, injected *in situ*, produced a significant ($p<0.05$) inhibition of the MSTO-211H growth both *in vitro* and *in vivo*, and was even comparable to IP PTX treatment. Interestingly, the treatment with free MSCs ($5x10^5$), at a similar amount contained in around 1ml of MFAT, exerted only a little anticancer activity.