Low dose ionizing radiation induces tumor growth promoting factors in stress-induced premature senescent fibroblasts. Xiuquan Luo and David A. Boothman. [1]Dept.of Oncology, [2]Dept of Neuro Oncology, Program in Cell Stress and Cancer Nanomedicine, University of Texas Southwestern Medical Center at Dallas, TX 75390, USA. David.Boothman@UTSouthwestern.edu

Recent evidence suggest that the causes of cancer development are not limited to mutations within cancer cells, but also involve in alterations of cancer microenvironment. Senescent cells are irreversibly growth arrested, but remain metabolically active. Senescent cells, especially senescent fibroblasts in the stroma may provide a beneficial environment for tumor growth through secretion of certain factors. Accumulation of senescent cells in the stroma of patients repeatedly exposed to low doses of IR or low dose rates of IR, could be an important factor, causing alteration of the microenvironment that ultimately benefits tumor development. It is known that multiple and long-term exposure of low-dose ionizing radiation (IR) induces stress-induced premature senescence (SIPS) in both stromal and tumor cells. Thus. low-dose IR exposure might promote cancer growth due to microenvironment changes through factors secreted by induced SIPS cells. We hypothesize that accumulation of senescent fibroblasts due to low-dose IR exposure would lead to alterations of microenvironment that could promote cancer growth and progression.

In our recent studies, we found that expression of insulin-like growth factor 1 (IGF-1) and secretory clusterin (sCLU) were increased in senescent fibroblasts, and increased sCLU expression in senescent fibroblasts was mediated through IGF-1/IGF-1R/MAPK/Egr-1 signaling. As we previously reported, the same signaling pathway mediates sCLU induction after IR exposure, wherein expression was prevented by the IGF-1R inhibitor, AG1024. Further studies showed that, although IR treatment induces sCLU in young fibroblasts, it does not further increase sCLU expression in senescent fibroblasts. Additionally, fibroblasts from *Ataxia telangiectasia* (AT) patients express low basal sCLU levels (from IGF-1 in media), but importantly, sCLU was not increased during senescence or after IR exposure. Our results also show that ATM inhibitor, AAI, inhibits both IGF-1 and sCLU expression in senescent fibroblasts. These results suggested that ATM is upstream of senescence induced sCLU expression.

We also established a co-culture mouse model *in vivo* by co-injection of cancer cells with young or senescent normal fibroblasts into mice subcutaneously. We found that MDA-MB-231 breast cancer cells co-injected with human normal senescent fibroblasts developed larger tumors than cancer cells co-injected with the same amount of young fibroblasts. Similar results were observed using A549 lung cancer cells. Since increased IGF-1 signaling is reported to be a poor prognostic factor of breast cancer and over-expression of sCLU protects cells from various stresses that induce apoptosis, it is possible, that senescent fibroblasts generated after low dose IR exposure create a favorable environment for cancer cell development through IGF-1-sCLU secretion. Further studies will be performed to test the role of senescent fibroblast-induced IGF-1-sCLU induction in tumor development. Altering IGF-1 or sCLU levels by genetic and pharmacological approaches may prevent this low dose IR-induced tumor promoting pathway. Examining long-lived IGF-1-sCLU expression may be a risk factor.

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