ImmunoTools *special* Award 2022

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Investigation of the epigenetic basis of the late on-set adverse effects of radiotherapy in cancer patients

Background

Radiotherapy (RT) is substantially considered as a key treatment in breast cancer and approximately is applied to > 70% of cancer patients. It has been reported that ~95% of cancer patients with RT developed radiodermatitis. Late on-set adverse effects (LAEs) include fibrosis, chronic ulcer, and secondary skin tumors, which develop months to years after RT. Unlike the majority of cases of acute radiodermatitis, LAEs are unlikely to be self-repairing and the contributing reasons remain undetermined.

Efforts to explain the mechanisms of frequent LAEs due to RT by genetic variation remain largely inconclusive. Recently, ionizing radiation has been shown to alter the epigenome, which comprises biochemical markers and regulatory molecules controlling genomic activity without changes in the DNA sequence. The alterations in cellular epigenetic architecture can have long-lasting effects on gene expression, and, therefore, may constitute significant mechanisms mediating the LAEs of RT.

Recent studies have shown that in addition to immune cells (Netea et al., 2016), epidermal stem cell (EpSC) have also been discovered to harbor a memory of previous injuries, which enables the skin to respond to subsequent assaults swiftly. Such inflammatory memory is carried out by maintaining the accessibility of the chromatin regions of several key stress response genes to transcription factors (TFs) (Naik et al., 2017).

Aim

The proposed project aims to identify the functional and molecular differences between the irradiated and non-irradiated skin-derived EpSC.

Research plan

We have collected skin biopsies from the non-irradiated (non-RT) and irradiated sites (RT) of breast cancer patients receiving radiotherapy one to five year ago. We plan to purify and quantify EpSC from the skin samples using fluorescence-activated cell sorting. Then we will perform deep RNA-sequencing to identify differentially expressed genes between the non-RT and RT EpSC. In this gene expression profiling, we will in particularly focus on TFs that are differentially expressed and have their targets enriched in the differentially expressed genes. Because TFs may function as master regulators in gene expression in response to injury (Sawaya et al., Antonini et al.). Next, we will treat the non-RT and RT EpSC with different cytokines and growth factors that have been shown to be important for skin homeostasis and wound healing, e.g., IFN-γ, IL-1, IL-6, TNF-α, TGF-β, EGF, FGF, KGF, IGF, GM-CSF. We will examine if the non-RT and RT EpSC respond differently to these stimuli, in regarding to gene expression, colony formation, proliferation, migration, differentiation, and inflammatory response. Furthermore, we will trace down the signalling pathways and TFs underpinning the different response of the non-RT and RT EpSC. To this end, we will perform western blotting or reporter assays to detect the activation of individual signalling pathways in EpSC treated with specific cytokines and growth factors.

ImmunoTools cytokines and growth factors will be used for this part of the study. This work will provide new knowledge about the molecular mechanisms underlying the late on-set adverse effects of radiotherapy in cancer patients. The insights gained from human samples bridge the gap of bench-to-bedside and likely to impose a direct impact on clinical diagnosis and treatments.

Reference

Mihai G. Netea et al., “Trained Immunity: A Program of Innate Immune Memory in Health and Disease,” Science (New York, N.Y.) 352, no. 6284 (April 22, 2016): aaf1098.

Shruti Naik et al., “Inflammatory Memory Sensitizes Skin Epithelial Stem Cells to Tissue Damage,” Nature 550, no. 7677 (October 26, 2017): 475–480.

Andrew P. Sawaya et al., “Deregulated Immune Cell Recruitment Orchestrated by FOXM1 Impairs Human Diabetic Wound Healing,” Nature Communications 11, no. 1 (September 16, 2020): 4678.

Dario Antonini et al., “A Composite Enhancer Regulates P63 Gene Expression in Epidermal Morphogenesis and in Keratinocyte Differentiation by Multiple Mechanisms,” Nucleic Acids Research 43, no. 2 (January 2015): 862–874.