Wounding triggers invasive progression in human basal cell carcinoma

Background

Basal cell carcinoma (BCC) is the most common human cancer and often displays a spectrum of non-invasive (nodular) to invasive (infiltrative) patterns. Although BCC is predominantly driven by aberrant Hedgehog (HH) signaling, treatment-resistant forms frequently exhibit additional cellular dysregulation. These tumors harbor distinct cellular states linked to local invasion and potential therapy resistance. This study investigated how wound-healing responses could trigger a shift in both cancer cells and surrounding fibroblasts toward an invasive phenotype, raising important questions about how injury from biopsies could promote aggressive BCC progression.

Research Questions

- How does gene expression in BCC cells differ between nodular and infiltrative states?
- What gene expression changes occur in BCC cells and tumor-associated fibroblasts upon tissue wounding by biopsy?
- Are wound responses linked to HH inhibitor resistance?
- Can spatially resolved transcriptomic tools (e.g., CosMx SMI) help uncover the individual cellular changes that underlie these wounding processes in human tumor samples?

Results & Conclusions

- **Identification of gene programs:** Single-cell analysis and spatial transcriptomics uncovered seven dominant transcriptional "meta-programs" in BCC cancer cells, one of which strongly associated with invasive tumor regions and included wound-response genes.
- **Link to wounding:** In both naturally ulcerated and experimentally wounded BCCs, cancer cells near the wound site quickly switched from a nodular to an invasive transcriptional state, mirroring the pattern seen in highly infiltrative and treatment-resistant BCCs.
- **Link to HH inhibitor resistance:** This wound-associated state is also seen in tumors that become less dependent on HH signaling, helping explain how wounding may lead to HH inhibitor resistance.
- **Fibroblast reprogramming:** Alongside cancer cells, a wound-responding cancer-associated fibroblast (CAF) state emerged that shares many features with fibroblasts in chronically infiltrative tumors, suggesting a stable, pro-invasive microenvironment is established after injury.
- **Therapeutic implications:** Because invasive reprogramming occurred in a short time span following biopsy, these data raise questions about whether wound-inducing procedures (e.g., biopsies, certain local therapies) may inadvertently accelerate local invasion or facilitate treatment resistance in residual BCC cells.

Oncology CosMx® Spatial Molecular Imager (SMI) Case Study

Sample Type	FFPE BCC samples, including tissue before and after punch-biopsy wounds
Tissue Type	Human skin tumor tissue from surgical or biopsy specimens
Assay	CosMx 6K RNA Panel
Analyte	RNA
Instrument	CosMx SMI (new spatial data) and GeoMx® DSP (prior data)

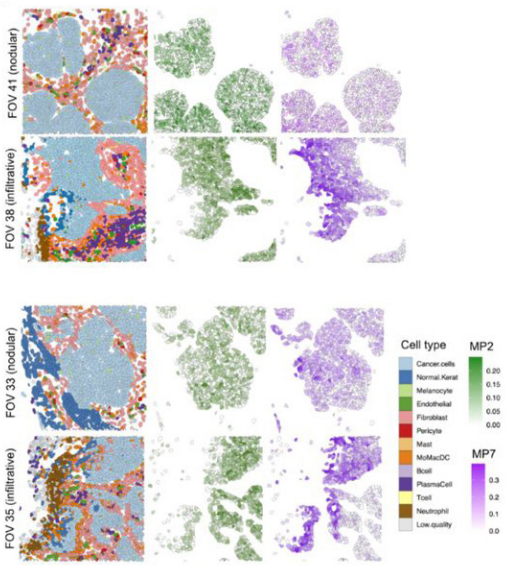

Figure 2G: Spatial Molecular Imaging of BCC. Example nodular and infiltrative tumor areas, with cell type composition and spatial distribution of meta-programs MP2 and MP7 shown.

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