

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.

Experimental Setup

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)

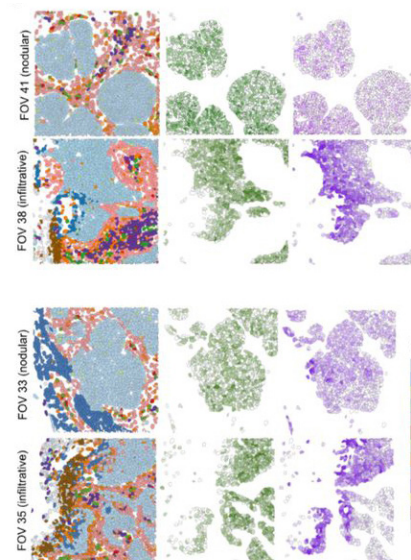


Figure 2G: Spatial Molecular Imaging of BCC. Example nodular and infiltrative tumor areas, with cell type composition and spatial distribution of meta-programs MP2 and MP7 shown.

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