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DERMATOLOGICA HELVETICA

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WHAT'S NEW

COL10A1 expression distinguishes a subset of cancer-associated fibroblasts in high-risk basal cell carcinoma

This section is a contribution from the SKINTEGRITY.CH interdisciplinary research consortium. The collaborative work was performed by Mauro Esposito and colleagues, including SKINTEGRITY.CH Principal Investigators Profs. Mitchell Levesque and Jürg Hafner, PD Dr. med. François Kuonen, and Dr. Gaetana Restivo, researcher and manager of the SKINTEGRITY.CH biobank.

Mauro Esposito. Basal cell carcinoma (BCC) is the most common cancer in humans. Although most BCCs can be removed by surgery or treated locally without complications, if left untreated this cancer can grow deep into the tissue or even metastasize. In advanced cases, systemic therapies using Hedgehog pathway inhibitors or immune checkpoint inhibitors might be considered.

BCCs can present as different morphological subtypes. These subtypes are associated with different risks of recurrence: superficial and nodular BCCs are considered low-risk subtypes while the micronodular, sclerosing and basosquamous subtypes have a high risk of recurrence. Interestingly, these subtypes do not show major differences in their mutational profile as most of them harbor driving mutations in the same molecular pathway. Therefore, a better understanding of how more aggressive BCC develops is needed. We hypothesized that the stroma surrounding the cancer cells and particularly cancer-associated fibroblasts (CAFs) influence growth patterns and invasiveness of BCC tumors. The influence of CAFs on cancer progression and therapy response has been reported for various other cancer types but is understudied in BCC. In order to investigate the influence of the stroma on BCC development, we collected a cohort of FFPE patient biopsies containing all of the histological subtypes mentioned above as well as healthy skin samples as controls and performed laser-capture microdissection

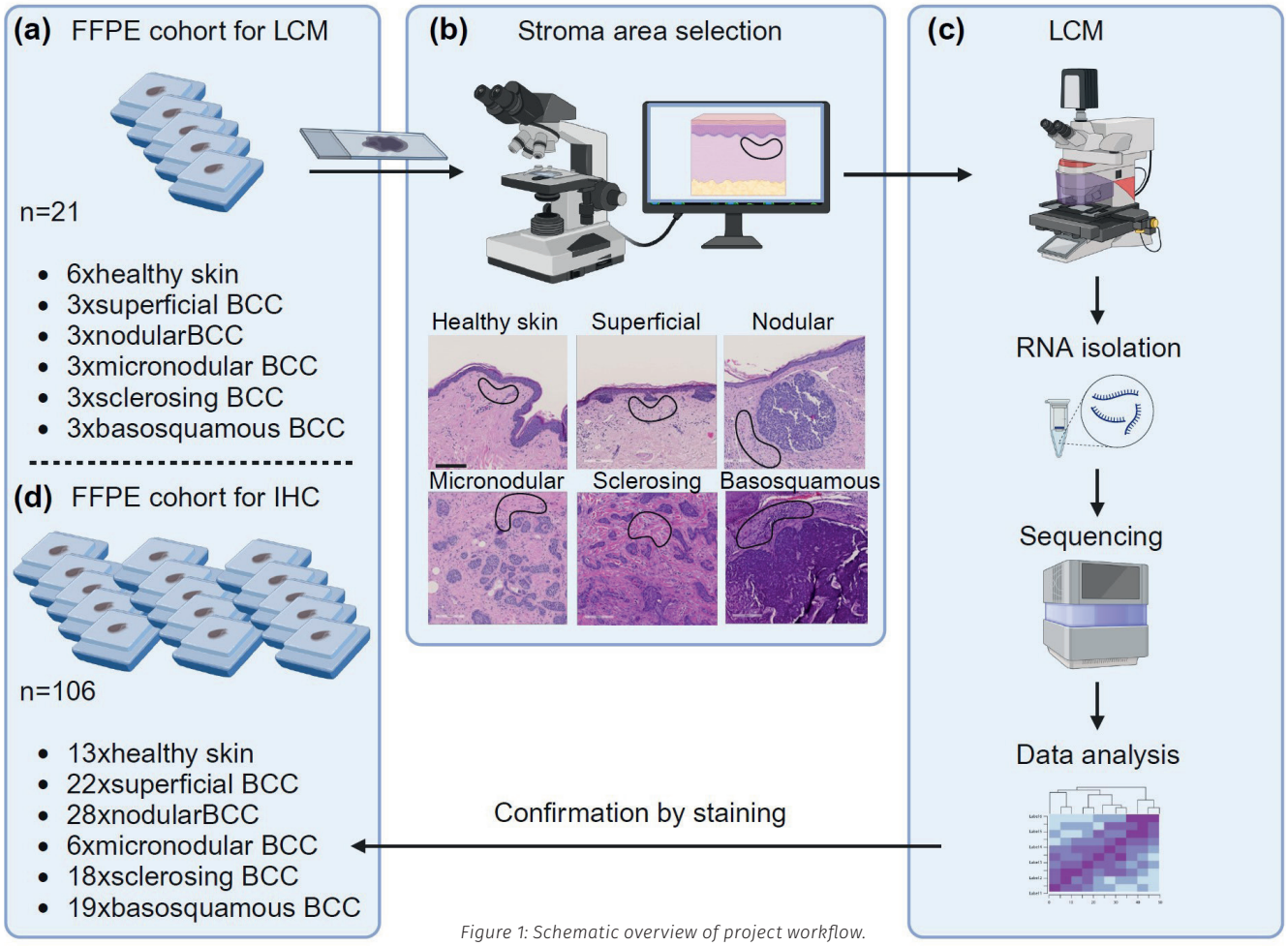

Figure 1: Schematic overview of project workflow.

(LCM) on tissue sections. LCM allowed us to excise stromal areas directly adjacent to cancer cells with a high spatial resolution. We then isolated mRNA from the micro-dissected tissue sections and performed RNA sequencing *(Figure 1)*. This revealed that BCC stroma (all subtypes) has a transcriptional profile that is different from healthy skin and that each subtype has its own distinct gene expression signature. When we compared gene expression between low- and high-risk subtypes, one of the few significantly upregulated genes in the high-risk group was *COL10A1* which codes for type X collagen, a type of short chain collagen normally expressed by chondrocytes during terminal differentiation.

To confirm *COL10A1* expression at the protein level, we performed immunohistochemistry on an extended cohort of BCC biopsies and could demonstrate a high abundance of this collagen, especially in the stroma of sclerosing and basosquamous tumors *(Figure 2)*.

In order to determine which cell type is mainly responsible for producing type X collagen, we used two existing single-cell RNAseq data sets created by our own lab (Restivo et al. 2022) and by our collaborator Dr. François Kuonen (CHUV). In both data sets, we found a specific subpopulation of fibroblasts to show high expression of *COL10A1*. Intriguingly, this *COL10A1*-high CAF subpopulation showed high expression of a stromal invasive niche signature defined by Yerly et al. in 2022. Moreover, this subpopulation was associated with extracellular matrix remodeling illustrated by the expression of factors such as *MMP11* and *COL11A1*. Using RNAscope on BCC tissue biopsies, we could confirm the presence of a stromal cell population co-expressing *COL10A1, COL11A1* and *MMP11* in situ. Although further studies are needed to elucidate the functional role of *COL10A1* in BCC biology, our findings indicate the potential use of *COL10A1* as a biomarker for high-risk BCC and highlight the importance of extracellular matrix components in BCC progression.

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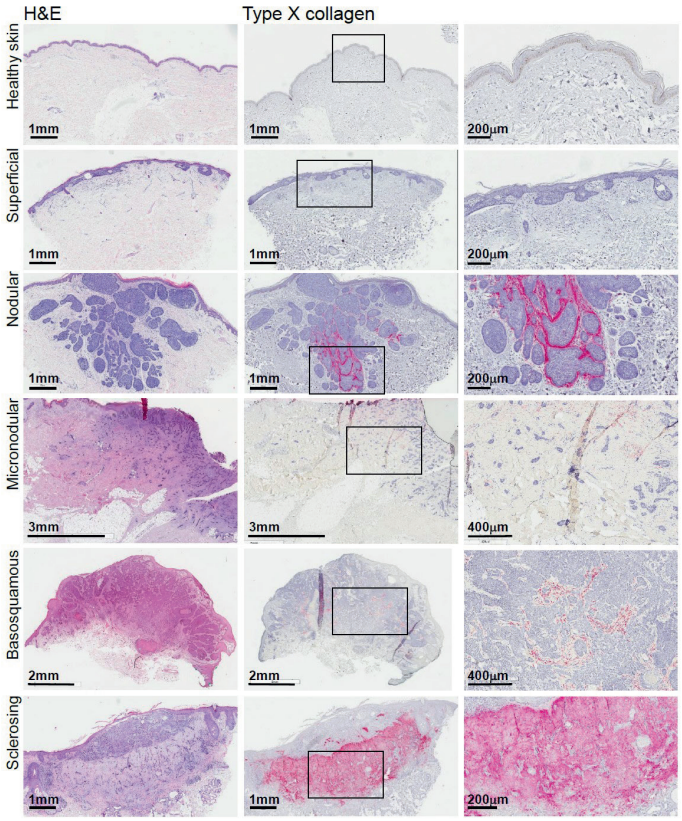
Reference

Esposito, M., Yerly, L., Shukla, P., Hermes, V., Sella, F., Balazs, Z., Lattmann, E., Tastanova, A., Turko, P., Lang, R., Kolm, I., Staeger, R., Kuonen, F., Krauthammer, M., Hafner, J., Levesque, M.P. & Restivo, G. (2024). COL10A1 expression distinguishes a subset of cancer-associated fibroblasts present in the stroma of high-risk basal cell carcinoma. Br J Dermatol, 191(5), pp. 775-790. https://doi.org/10.1093/bjd/ljae258



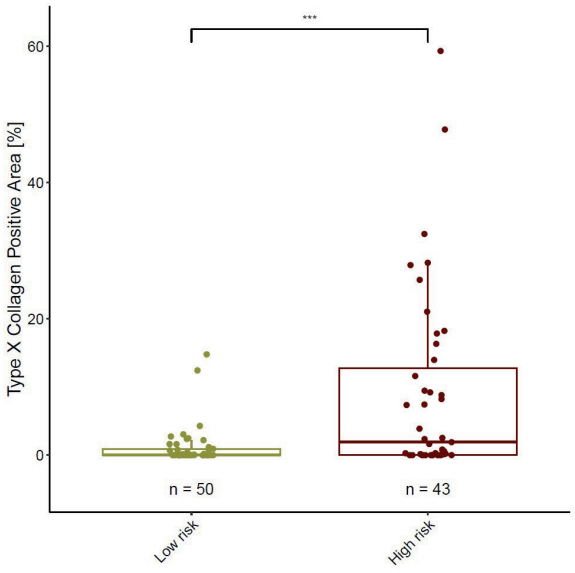


Figure 2: Immunohistochemistry using an antibody against collagen type X confirms COL10A1 *expression at the protein level in aggressive BCC tumors.*