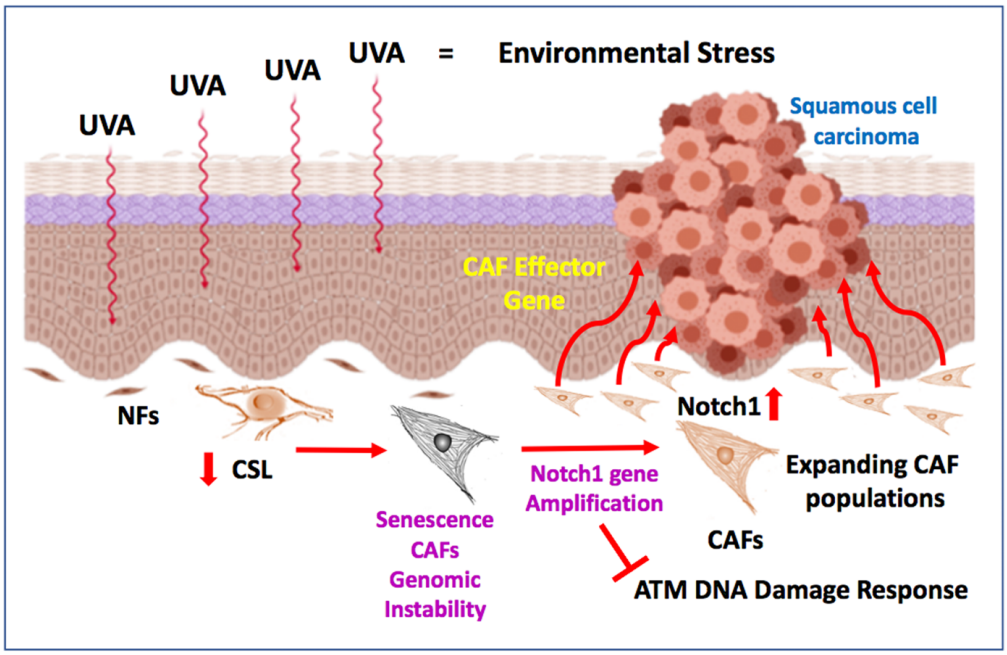
We have been focusing on the interconnection between skin aging and development of skin "*cancer fields*", i.e. multiple and recurrent cancer lesions linked with chronic sun exposure and patients' immune suppression. Our findings point to the existence of stromal cells genetic alterations with potential therapeutic implications.



- Genomic instability of CAFs results in selective expansion of subpopulation with NOTCH1 gene amplification.
- NOTCH1 amplification and increase expression blocks genomic instability induced growth arrest.
- NOTCH1 genetic or pharmacological inhibition of NOTCH1 activity suppresses cancer/stromal cells expansion.

ABSTRACT

Cancer associated fibroblasts (CAFs) are key component of the tumor microenvironment, which may differ among female versus male patients. Genomic alterations in these cells remain a point of contention.

We report that CAFs from skin Squamous Cell Carcinomas (SCCs) display chromosomal alterations, with heterogeneous *NOTCH1* gene amplification and overexpression that also occur, to a lesser extent, in dermal fibroblasts of apparently unaffected skin. The fraction of the latter cells harboring *NOTCH1* amplification is expanded by chronic UVA exposure, to which CAFs are resistant. The advantage conferred by *NOTCH1* amplification and overexpression can be explained by NOTCH1 ability to block the DNA damage response (DDR) and ensuing growth arrest through suppression of ATM-FOXO3a association and downstream signaling cascade. In an orthotopic model of skin SCC, genetic or pharmacological inhibition of NOTCH1 activity suppresses cancer / stromal cells expansion. Here we show that NOTCH1 gene amplification and increased expression in CAFs are an attractive target for stroma-focused anti-cancer intervention.

To which extent these findings apply to cancer / stromal cell evolution in female versus male patients is an important question for future studies.