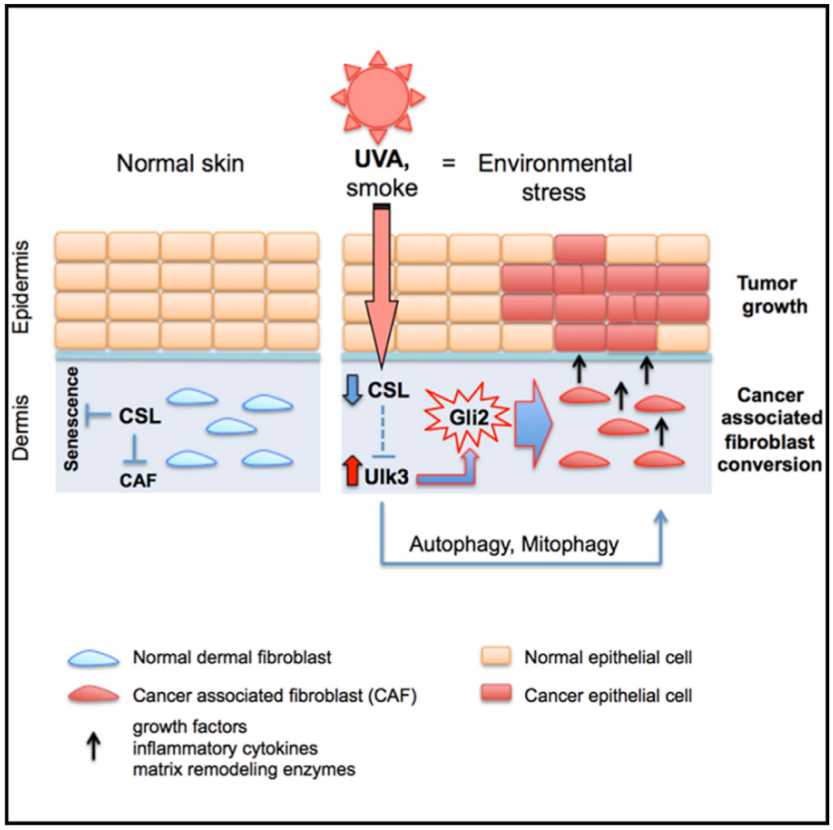
We have been focusing on the mechanism(s) of conversion from normal fibroblast to cancer associated fibroblast in the skin stroma. Our findings point to the existence of a new targetable stromal cell alteration with translational implications for skin field cancerization, a pathological condition with multiple and recurrent cancer lesions often linked with chronic sun exposure.

Graphical Abstract



HIGHLIGHTS

- CAF conversion by loss of CSL depends on Gli activation
- CSL functions as negative regulator of the pro-autophagy kinase Ulk3
- Increased Ulk3 induces Gli2-dependent CAF activation, separately from autophagy
- Silencing of Ulk3 in SCC-derived CAF suppresses their tumor-enhancing properties

Goruppi et al, Cell Reports, 2017 (link)

ABSTRACT

The connection between signaling pathways activating cancer associated fibroblasts (CAFs) remains to be determined. Metabolic alterations linked to autophagy have also been implicated in CAF activation. CSL/RBPJ, a transcriptional repressor that mediates Notch signaling, suppresses gene expression program(s) leading to stromal senescence and CAF activation. Deregulated GLI signaling can also contribute to CAF conversion.

Here we report that compromised CSL function depends on GLI activation for conversion of human dermal fibroblasts into CAFs, separately from cellular senescence. Decreased CSL up-regulates the expression of the ULK3 kinase, which binds and activates GLI2. Increased ULK3 also induces autophagy, which is unlinked from GLI and CAF activation. ULK3 up-regulation occurs in CAFs of several tumor types and ULK3 silencing suppresses the tumor enhancing properties of these cells. Thus, ULK3 links two key signaling pathways involved in CAF conversion and is an attractive target for stroma-focused anti-cancer intervention

Dysregulation of autophagy has been linked to neurological, cardiovascular and mitochondrial diseases with sex-based differences in autophagy regulation during the the lifespan leading to an increased risk of disease. To which extent our findings apply to stromal cell activation in female versus male patients is an important question for future studies.