Androgen receptor functions as transcriptional repressor of cancer-associated fibroblast activation

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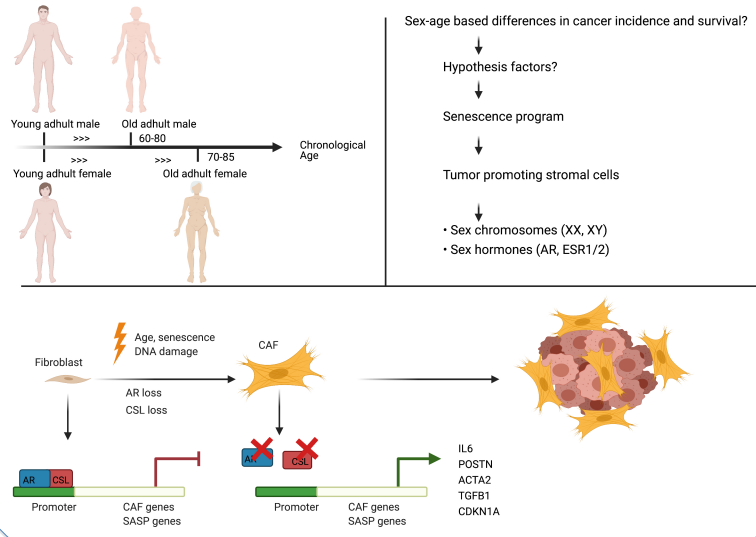
Abstract

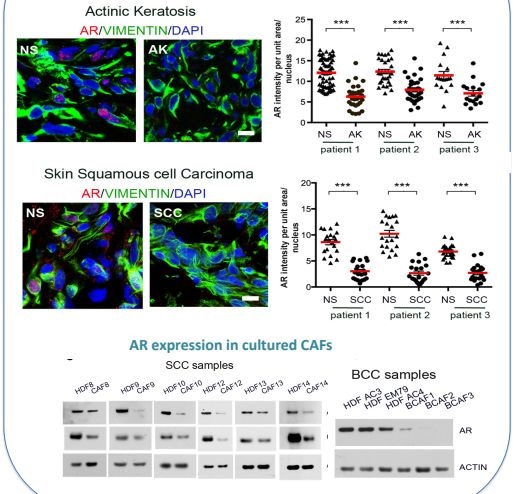
Aging and senescence have long been linked to cancer risk and development. Males and females greatly differ in the aging program, with females aging slower than males. A number of factors have been proposed to play a role, such as sex chromosomes and or sex hormones.

While these phenomena are more characterized in the epithelial compartment, little is known on the role of sex dimorphisms in the tumor stroma. We report that the level of the androgen receptor (AR) is lost in fibroblasts in preneoplastic lesions as well as in malignant lesions. Functionally, decreased AR expression in primary human dermal fibroblasts (HDFs) from multiple individuals induced early steps of cancer associated fibroblasts (CAFs) activation, and in an orthotopic skin cancer model, AR loss in HDFs enhanced tumorigenicity of cutaneous squamous cell carcinoma (SCC) and melanoma cells. Forming a complex, AR converged with CSL/RBP-Jκ in transcriptional repression of key CAF effector genes. Here we show that AR signaling is fundamental in order to prevent stromal fibroblasts activation into CAFs. This is of translational relevance in the era of personalized medicine because we have at our disposal an armory of drugs that can finetune androgen signaling. Furthermore, our findings point to the importance of sex-based differences which could offer more precise tumor-stroma based therapeutic approach.

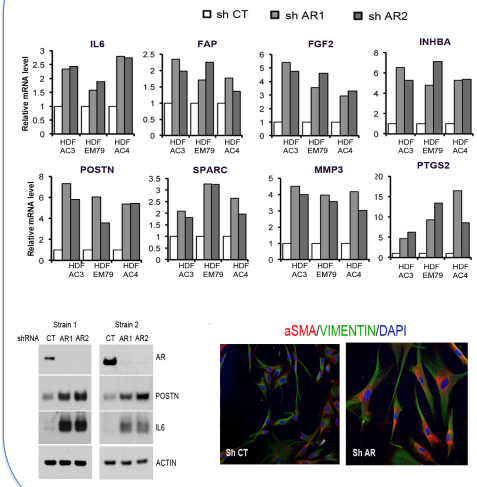
Graphical abstract



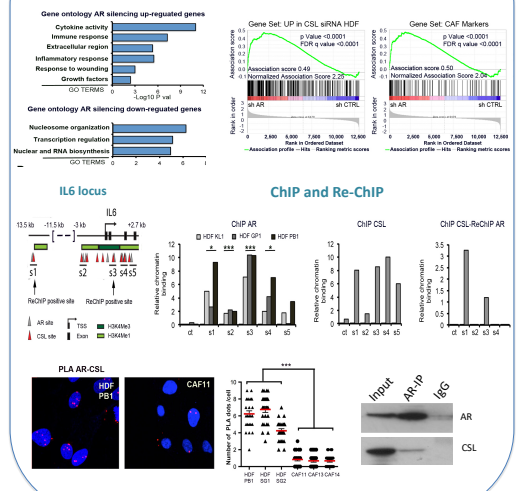
AR expression is reducedin premalignant and malignant skin cancer stroma



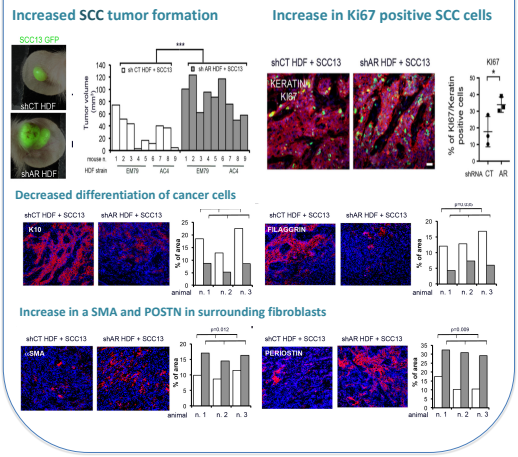
AR acts as suppressor of CAF activation



AR and CSL physically converge on negative control of CAF activation



HDFs with reduced AR expression promote SCC and melanoma formation



Summary

- AR is down modulated in the stroma of premalignant and malignant skin cancer lesions.
- Loss of AR in HDFs induces CAF activation.
- AR acts as repressor of CAF marker genes (in collaboration with CSL)
- AR silenced HDFs promote tumor growth *in vivo*.

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Lab members

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