Androgen signaling in skin cancer susceptibility

Cancer susceptibility of male versus female individuals is significantly different in many cancer types, including skin cancer (squamous and basal cell carcinoma, melanoma), with female populations generally showing lower incidence and/or greater survival than males (Clocchiatti *et al*, 2016). Besides occupational and/or behavioral factors, the role that hormonal and genetic/epigenetic differences play in cancer development in organs with non-reproductive functions is poorly understood.

The focus of the PhD student's project is on the role of the androgen receptor (AR) signaling pathway in control of skin cancer development by surrounding stromal fibroblasts.

AR signalling plays a double-edge sword role in cancer development. Levels of androgens decline with age in both male and female individuals, suggesting a possible link between decreased androgen receptor (AR) activity and the aging-associated increase in cancer risk. Organismal aging is intimately associated with senescence of cells in various tissues. While cellular senescence suppresses the oncogenic potential of cancer cells through irreversible withdrawal from the cell cycle, the same process in surrounding stromal fibroblasts can promote cancer development through induction of genes with a variety of pro-inflammatory and matrix remodelling functions, composing the so called *Senescence Associated Secreted Phenotype* (SASP). Expression of SASP genes is also a key feature of fully established cancer associated fibroblasts (CAFs) that we have shown to escape from cellular senescence through a combination of genetic and epigenetic mechanisms (Bottoni *et al*, 2019; Katarkar *et al*, 2020; Procopio *et al*, 2015).

AR activity is required for sustained growth of cancer cells, not only in prostate, but also other organs such as breast, lung, salivary gland and, in skin, melanoma (Ma *et al*, 2021). We have shown however that in stromal fibroblasts decreased AR activity triggers early steps of CAF activation with induction of senescence, SASP and, in an orthotopic model of skin squamous cell carcinoma (SCC) and melanoma, tumor expansion (Clocchiatti *et al*, 2018). A question of importance is whether there are mesenchymal-specific mechanism(s) in CAFs, which could be selectively identified to counteract the role that AR signaling plays in the whole cancer process. In ongoing work, we have identified a mesenchymal--specific transcriptional co-activator under AR control that can be targeted to selectively suppress CAF activation while not impining directly on cancer cells. The PhD student will focus on the molecular action of this molecule, starting from the transcriptomic and proteomic data that we have generated from cells plus/minus modulation of its expression. The student will utilize a combination of genetic, biochemical and *in vivo* assays available in the laboratory for mechanistic insights and assess the translational significance of the findings.

Cited references (representative laboratory publications)

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