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Abstract:	

Melanoma and the microenvironment: age matters

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Advancing age is a risk factor for cancer, and there is no doubt that the accumulation of DNA damage over time contributes to the correlation of age with cancer risk, as it increases the rate of oncogenic mutations in pre-cancerous cells, thus triggering cellular transformation. In addition, age-related changes in the immune system can result in reduced adaptive immunity and a pro-tumorigenic inflammatory microenvironment, which is fuelling tumor progression and contributes to poor prognosis in the elderly.

In melanoma skin cancer around 50% of cases are diagnosed in individuals older than 65, and while mutations in the main oncogenic drivers of melanoma (e.g. *BRAF*^{V600E}) have been linked to the age of patients[1], not much is known about the effects of an aged microenvironment. Recent work from the Weeraratna laboratory, reported by Kaur et al[2] has shed some light on how fibroblasts in an aging microenvironment can contribute to melanoma growth and progression.

Normal melanocytes reside at the basement membrane of the epidermal layer of the skin, and while they are usually not in direct contact with dermal fibroblasts, they are exposed to factors secreted by fibroblasts. During aging the architecture of the skin changes significantly (Fig. 1), and the fibroblasts have accumulated DNA damage and a higher tendency to senesce, which is correlated with an altered secretome[3].

Kaur et al addressed the role of the aged microenvironment by injecting mouse melanoma cells harboring the *Braf*^{V600E} driver mutation into immunocompetent young or aged mice. Surprisingly, the tumors in aged mice grew much slower than in young mice, but the aged environment favored a more aggressive phenotype with increased angiogenesis and a higher number of lung metastases (Fig. 1). Corroborating observations were made in skin-reconstructs containing fibroblasts from either young (<35) or aged (>55) individuals, where aged fibroblasts had a profound pro-invasive effect on melanoma cells.

The detailed analysis of these aged fibroblasts revealed a variety of properties that not only contributed to the pro-metastatic activity, but also interfered with the efficacy of BRAF^{V600E} targeting therapy. Aged fibroblasts produced high amounts of sFRP2, a secreted protein, which was detectable in the serum of aged mice and when administered to young mice enhanced tumor angiogenesis and lung metastasis in the *Braf*^{V600E} model. In addition, aged fibroblasts secrete lower levels of scavengers of reactive oxygen species (ROS). This means, that aged fibroblasts allow increased induction of oxidative stress in melanoma cells. This was further amplified by sFRP2, which reduces the ability of melanoma cells to respond to oxidative stress. Overall, aged fibroblasts induce a high level of oxidative stress in melanoma cells and this produces DNA damage. Importantly, enhanced oxidative stress and DNA damage have not only been linked to a more aggressive phenotype, but also to resistance to BRAF targeting therapy. Indeed, Kaur et al show that in aged mice the BRAF-inhibitor response of the slow growing *Braf*^{V600E} melanoma allografts is reduced, and that aged fibroblasts protect melanoma cells from inhibitor action.

The clinical relevance of this study is supported by data showing significantly higher serum levels of sFRP2 in aged patients (>55) compared to younger patients (<40). Furthermore, melanoma samples from aged patients showed reduced expression of oxidative stress regulators and increased expression of DNA damage markers, a crucial finding that should be evaluated for its correlation with disease stage (and hence progression). In the context of BRAF targeted therapy, the authors assessed the correlation of patient age with therapy response in a cohort of 79 patients, with the idea that response might be decreased in aged patients. Choosing a cutoff of 65 years revealed a significant difference in therapy response.

In summary, Kaur et al reveal a novel molecular link, involving SFRP2 that connects patient age with progression and therapy response in melanoma. It is nevertheless currently uncertain whether sFRP2 could serve as biomarker for BRAF-inhibitor efficacy, as the patient-cohort was too small to see a statistically significant correlation of sFRP2 levels and therapy response. The authors also suggest the use of antioxidants in aged melanoma patients. Such an approach however will require further investigation, as in young (immunodeficient) mice antioxidants can promote experimental metastasis[4]. In conclusion, considering age in the design of future therapies might lead to an improvement.

References

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Figure 1: Aged shows major alterations including degenerated dermal collagen fibers and smoothening of the dermal/epidermal junction. Fibroblasts in aged skin produce an altered secretome, and whereas young fibroblasts produce scavengers of reactive oxigen species (ROS) such as SOD3 and PRDX6, this expression is reduced in aged fibroblasts. Young fibroblasts therefore protect melanocytes (as well as melanoma cells) from oxidative stress induced by ROS. In aged environment, aged fibroblasts do not protect from ROS and produce sFRP2 instead. This increases intracellular ROS, which leads to increased DNA damage. Cells with increased ROS and DNA damage are more aggressive, and while they grow slower and produce smaller tumors, they have a higher metastatic potential.

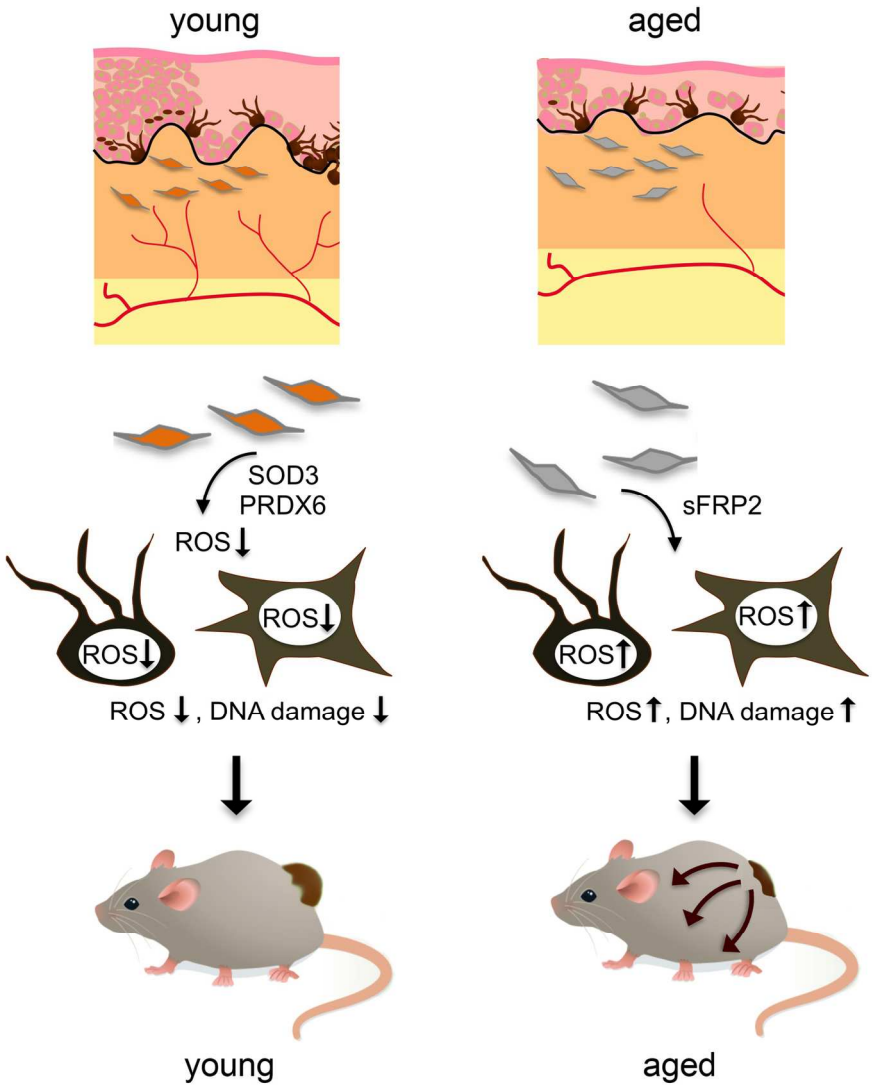

Figure 1
145x188mm (300 x 300 DPI)