CELLULAR INTERCONNECTIVITY IN REGENERATION: A PIONEERING STRATEGY FOR HEALTHY SKIN

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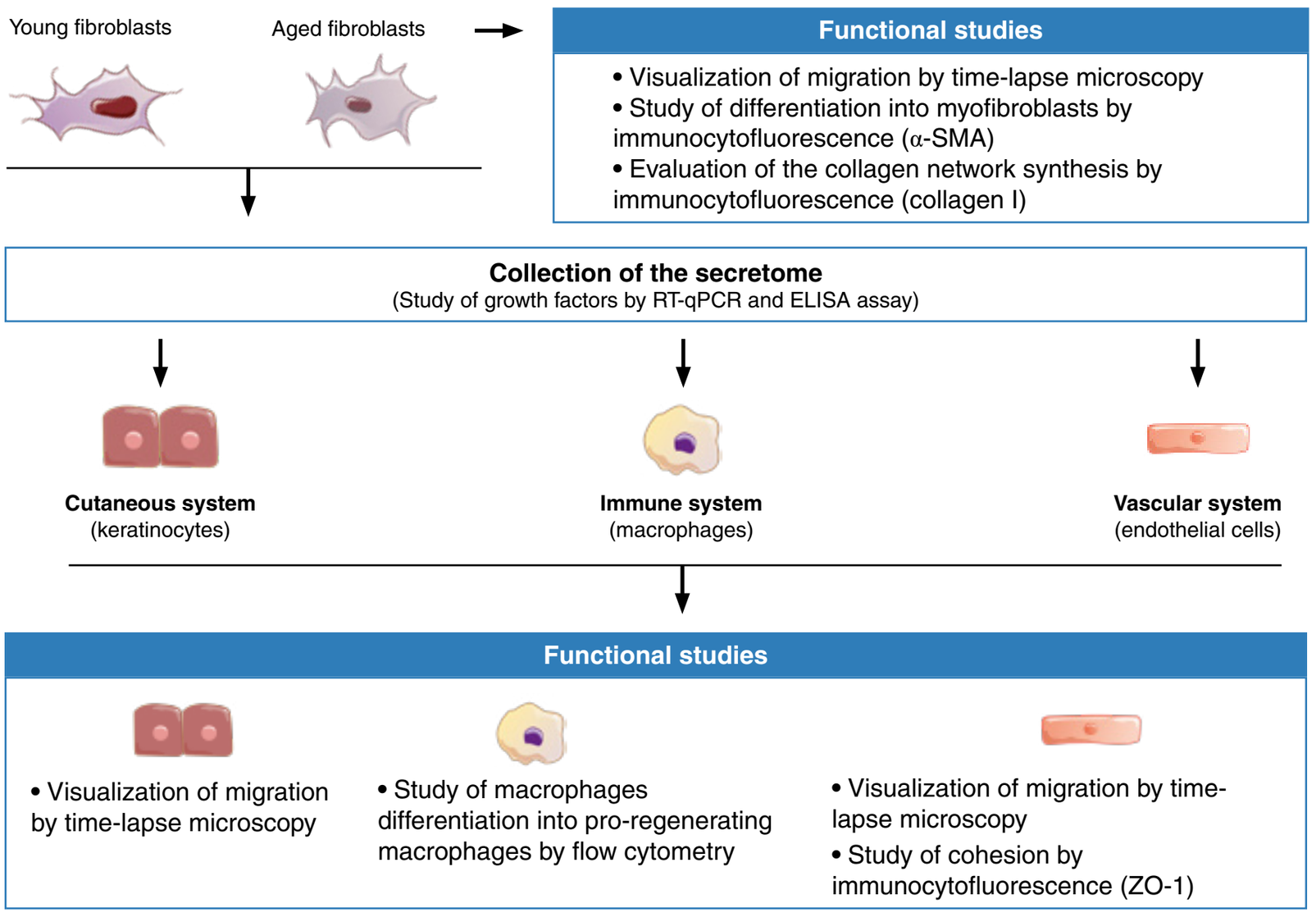
INTRODUCTION

Skin regeneration was for a long time restricted to re-epithelialization depending on keratinocytes and dermal matrix restructuring carried out by fibroblasts [1]. Recent scientific advances shed to light that regeneration is a more complex process requiring the intervention of cutaneous, vascular, and immune systems. Indeed, a population of pro-regenerating macrophages stimulates extracellular matrix remodeling [2], and the vascular network allows the supply to the skin of elements favoring its regeneration like nutrients, cells, and mediators [3]. These three major biological systems are interconnected by the fibroblast, which orchestrates the stages of the regenerating process through the secretion of a specific pool of growth factors, named fibroblast regenerating complex. This latter positively regulates the activity of keratinocytes, fibroblasts, endothelial and immune cells, for an optimal and global regenerating effect [4,5]. To this date, evolutions of cutaneous, immune and vascular interconnectivity in regeneration with aging is poorly described.

The objective of this study was to evaluate the modifications of the fibroblast regenerating complex with aging and the consequences on cutaneous, immune and vascular systems.

MATERIAL & METHODS



RESULTS & DISCUSSION

1. Study of the impact of aging on the composition of the fibroblast regenerating complex and on the functionality of fibroblasts

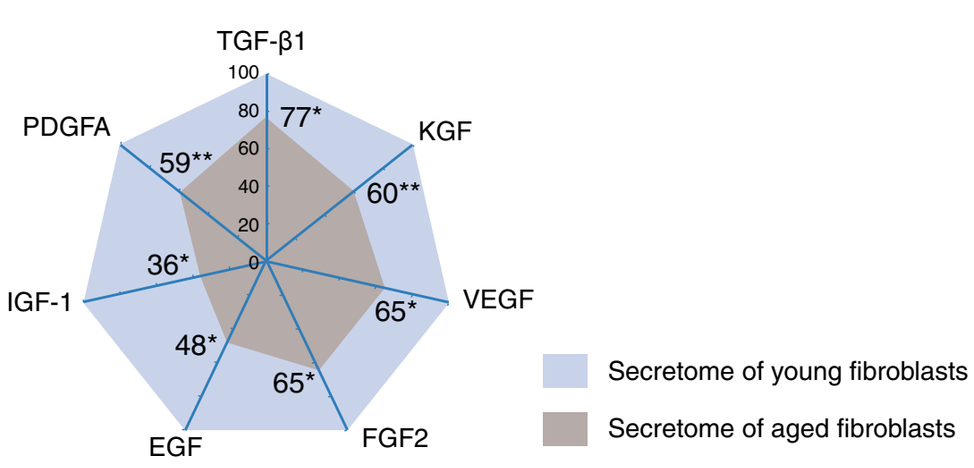


Figure 1. Changes in the levels of growth factors composing the fibroblast regenerating complex with aging. **: P<0.05; **: P<0.01*

The analysis of the impact of aging on the composition of the fibroblast regenerating complex revealed a reduced capacity of aged fibroblasts to express or synthesize all growth factors. The results showed a significant decrease of KGF by 40%, EGF by 52%, IGF-1 by 64%, FGF2 by 35%, PDGFA by 41%, TGF-β1 by 23% and VEGF by 35% in the secretome of aged fibroblasts in comparison to young fibroblasts (Figure 1).

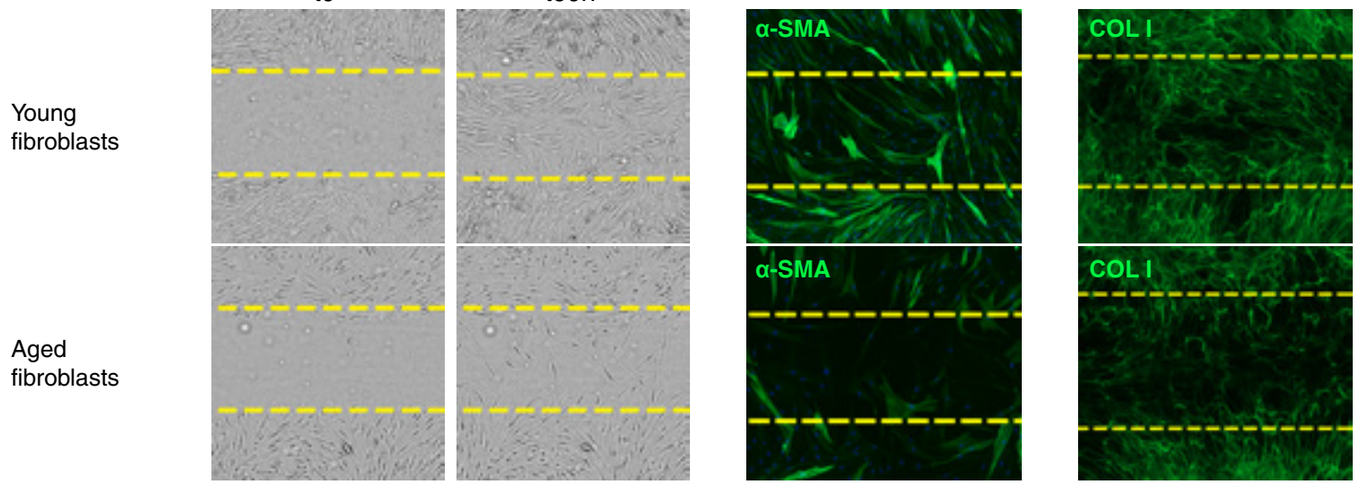


Figure 2. Impairment of fibroblast pro-regenerating activities with aging. A. Reduction in the capacity to recolonize a wounded area after 60 hours. B. Decrease of the expression of the α-SMA protein. C. Decrease of the synthesis of a collagen I network.

Results also showed that aging has a harmful effect on the metabolism of fibroblasts since aged fibroblasts displayed a reduction in the capacities of migration by 27% (P<0.05) (Figure 2A), differentiation into myofibroblasts by 75% (P<0.001) (Figure 2B) and synthesis of collagen I network by 43% (P<0.001) (Figure 2C), compared to young fibroblasts.

2. Study of the consequences of the regenerating complex depletion on the functionality of cutaneous, immune and vascular system

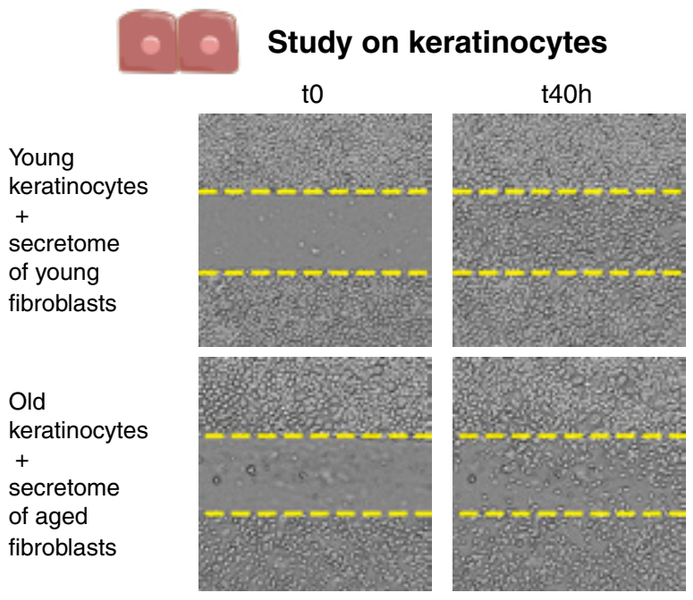


Figure 3. Impact of the secretome of aged fibroblasts on the capacity of keratinocytes to recolonize a wounded area after 40 hours.

Migration experiments demonstrated that the depletion in growth factors significantly impedes the ability of old keratinocytes treated with the secretome of aged fibroblasts to recolonize a wounded area by 45% (P<0.01), compared to young keratinocytes (Figure 3).

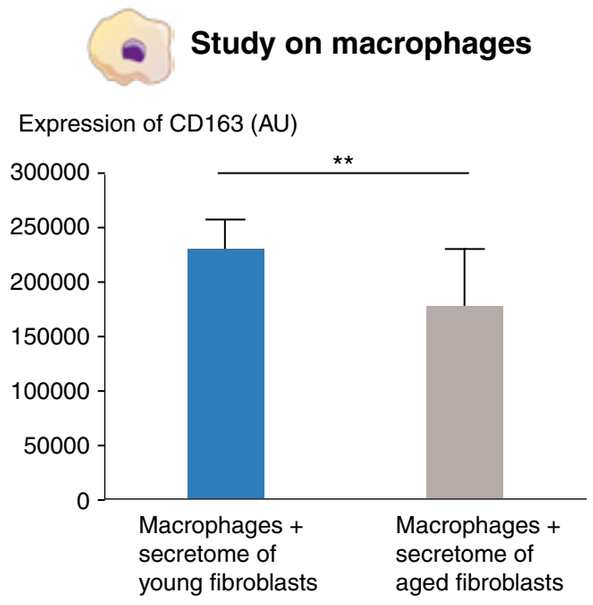


Figure 4. Decrease of the pro-regenerating population of macrophages after the treatment with the secretome of aged fibroblasts (Expression of CD163, **: P<0.01).

Macrophages treated with the aged secretome significantly lose their ability to differentiate into pro-regenerating macrophages by 23% (P<0.01) (Figure 4).

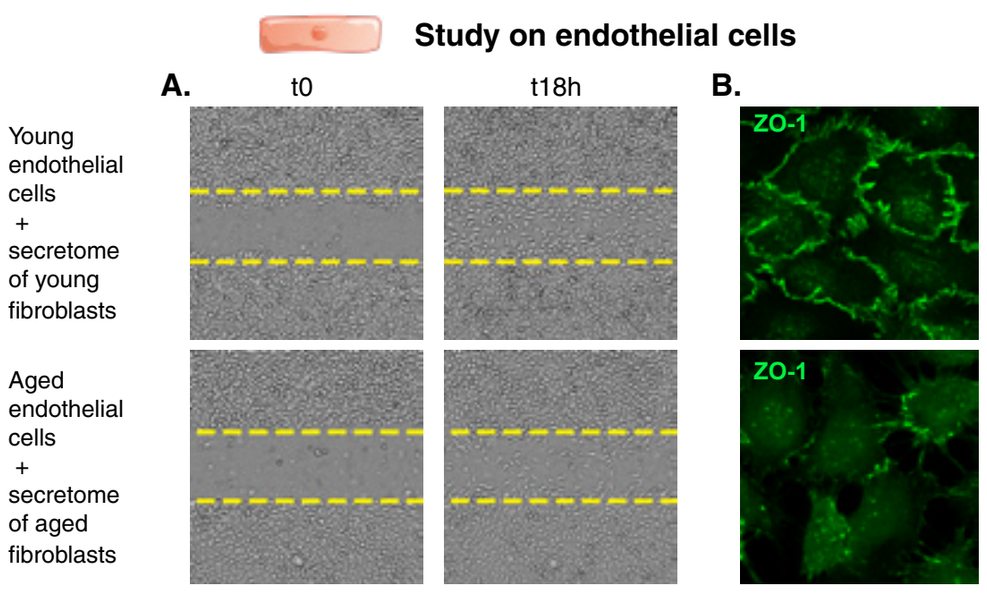


Figure 5. Negative impact of the depletion of the fibroblast regenerating complex on vascularization steps. A. Alteration of the capacity of aged endothelial cells treated with the aged secretome to recolonize a wounded aera after 18h. B. Decrease of the expression of the protein ZO-1 by aged endothelial cells treated with the aged secretome.

In response to treatment with the secretome of aged fibroblasts, the migration capacities of aged endothelial cells were impaired by 47% (P<0.001) (Figure 5A). Moreover, results showed that in the aged model the cohesion of endothelial cells is significantly reduced by 52% (P<0.001), demonstrating the negative impact of the aged secretome on the integrity of the vascular system (Figure 5B).

CONCLUSIONS

• This work demonstrated that in comparison to young cells, **aged fibroblasts exhibit a significant reduced capacity to express and synthesize the pool of growth factors composing the fibroblast regenerating complex**. This depletion in growth factors is accompanied by a **drastic alteration of their dermal restructuring-associated activities** (migration, differentiation in myofibroblasts and synthesis of collagen I network).

• The second part of the study highlighted that **the exhaustion of the regenerating complex in growth factors has a profound impact on the interactions of fibroblasts with their environment.** Indeed, **the interconnectivity of the cutaneous, immune and vascular systems is disrupted and this has deleterious functional consequences** on : 1/ the migration abilities of keratinocytes, 2/ the pro-regenerating activity of macrophages, 3/ the activity of endothelial cells and the cohesion of the vascular system, leading to regeneration defects and consequently to skin aging. This work emphasizes the **key role of this regenerative complex in maintaining interconnectivity and functionality of cutaneous, immune and vascular systems during regeneration process with aging**.

• Based on these discoveries, SILAB has developed a natural active ingredient composed of particular oligo-glucans from *Saccharomyces cerevisiae* that revitalizes the interconnectivity of the three biological systems by the endogenous production of a growth elixir able to reactivate the regeneration process for an anti-aging effect.

References:
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