Using Signaling Pathway Activation Analysis to Identify Prospective Drugs that May Slow Down or Reverse the Effects of Skin Aging and Photoaging

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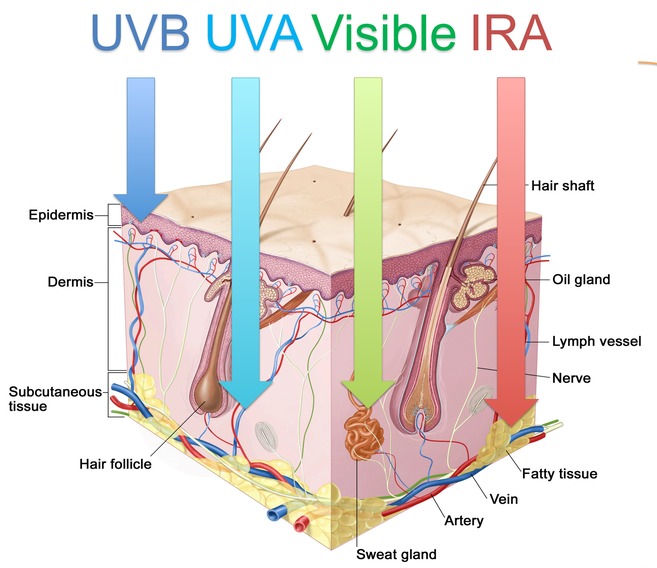
Introduction

Aging of the skin is developed due to the combination of the effects of time (intrinsic aging) and environmental factors (extrinsic aging). Extrinsic aging is caused primarily by ultraviolet light.



- DNA damage
- ROS formation
- Immunosuppression
- Inflammation
- Extracellular matrix remodeling
- Signal transduction pathways alteration

Skin (photo)aging
Cancer

The pathophysiological process of photoaging and skin aging derives largely from aberrant regulation of a multitude of finely tuned molecular mechanisms. Our goal is to expand the knowledge regarding relevant signal transduction pathways to provide opportunities for the novel therapeutic interventions to prevent and repair age-related skin damage. The promise of this research is the bioinformatical development of new drugs that target critical mediators of skin aging.

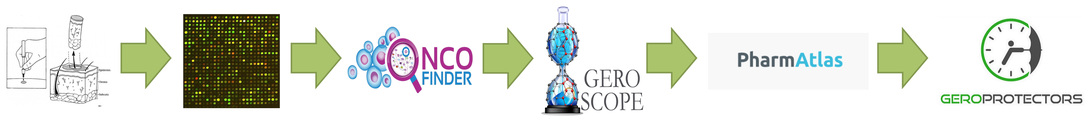
Purpose

To analyze signaling pathway activation in aged and photoaged skin in order to identify prospective drugs that may slow down or reverse the effects of skin aging and photoaging.

Materials & Methods

We used publically available datasets from GEO:

- GSE18876 - 78 samples for skin aging (45-86 years old) compared with norms (22 years old)
- GSE22083 - 98 samples for skin photoaging (UVA and UVB) compared with norm (not exposed)



Punch biopsy → MicroArray gene expression data → PAS calculation and normalization → Drug scoring and drug repurposing → Calculation of drug adverse effects → Association with geroprotective activity

Results

Signaling pathway activation analysis showed negative correlation between skin aging and photoaging, but these two processes share common pathways that can be potential targets for treatment.

We evaluated the activity of over 40,000 compounds for their ability to mimic signaling pathway activation profiles of young skin to make the shortlist of potential candidate drugs.

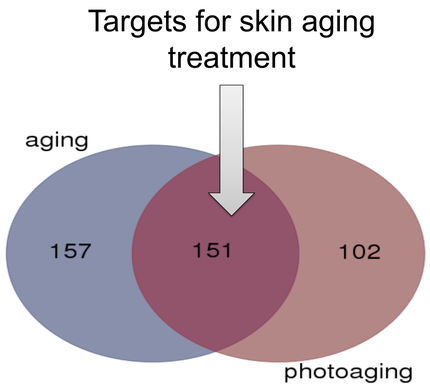


Fig. 1. The number of significantly dysregulated pathways during aging-photoaging.

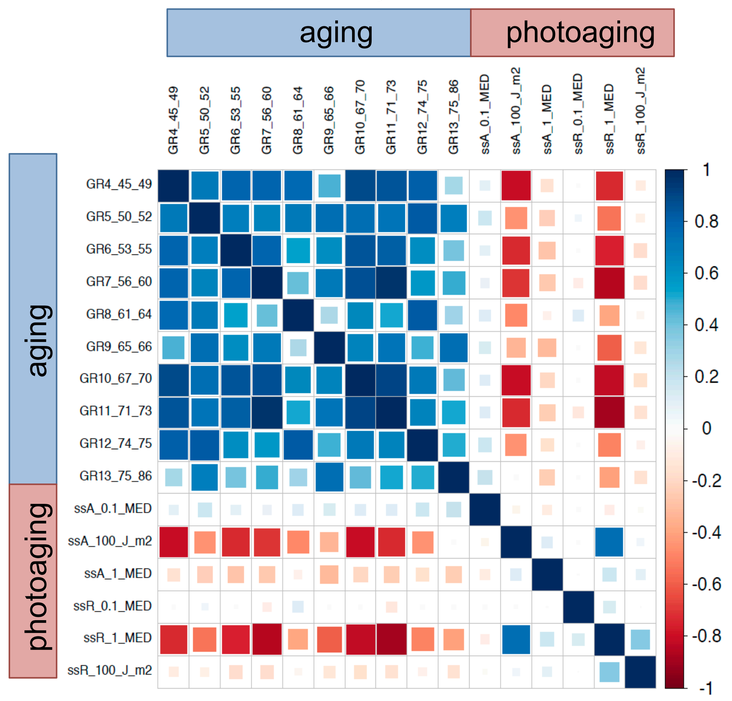


Fig. 2. Correlation plot of significantly dysregulated pathways between aging and photoaging.

Table 1. Top-7 potential treatments for aging skin.

Compound	DS	Classification	Geroprotective activity (max lifespan)	On the market as a skin care product	Top predicted side effects	ROR
Triptolide	191	NF-kB inhibitor	-	-	-	-
Staurosporine	189	Inhibitor of protein kinases	D.melanogaster, 35 %	-	-	-
CD437	174	Synthetic retinoid (retinoic acid receptors agonist)	-	Prevents UVB induced sebum production	-	-
Trichostatin A	171	Histone DeAc	D.melanogaster, 38 %	-	-	-
Ashwanghanda (Withaferin A)	169	Inhibitor of vimentin, NF-kB, Sp1 TF	-	Skin anti-cancer drug	-	-
Tretinoin	169	Retinoid Antioxidant	-	Acne, keratosis, photoaging treatment	Acute promyelocytic leukaemia	89342
					Plasmacytoma	61920
					Pustular psoriaris	59726
Phloretin	162	Inhibits the active transport of glucose into cells, antioxidant	-	Photoaging treatment	-	-

Conclusion

The pathophysiological process of photoaging and skin aging derives largely from dysregulation of signaling pathways. The promise of this research is the development of new drugs that prevent skin aging and photoaging.

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