Opinion about Usman PP paper

This is ana interesting review article about the role of micro RNAs in skin aging and its potential therapeutic interventions. I have only major concern and minor concerns.

My concern is the lack of comments about the interaction of the somatotrophic system (the somatotropic axis and the extrapituitary circuits) in the skin aging, as described in a model of congenital isolated growth hormone deficiency (IGHD). In addition, it was shown a significant regulation of age-related miRNAs in these human subjects with untreated lifetime IGHD. These miRNAs have an important overlap with serum-regulated miRNAs in GH-deficient mice, which have a remarkable extension of healthspan and lifespan. Importantly, predicted target genes for serum-regulated miRNAs in IGHD patients contribute to insulin, inflammation, and aging-related pathways, such as mTOR and FoxO pathways. These main up-regulated aging-related miRNAs,miR-100-5p,miR-195-5p,miR-181b-5p,and miR-30e-5p,were found to regulate in vitro expression of the age-related genes mTOR, AKT, NFκB, and IRS1, which also can be implicated in skin aging . For instance, miR-181b- 5p was up-regulated by approximately sevenfold in IGHD humans and the effect was even more pronounced in older individuals. This miR-181b overexpression inhibits cell proliferation, migration, invasion, and tumorigenesis by targeting IGF-1R and its downstream signaling pathways (Shi et al., 2013). Therefore, besides preventing inflammation and diabetes, miR-181 has a tumor suppressor effect, all key factors in age-related mortality. Conversely, miR-181b expression is increased in human senescent keratinocytes, suggesting tissue-specific proprieties of this miRNA (Rivetti di Val Cervo et al., 2012). I think that this submitted and good article will be enriched with a paragraph with these data, demonstrating again the role of these micro RNAs in aging in general and in the skin aging. Please see this related papers

1) Barros-Oliveira CS, de Jesus MJM, Campos VC, Salvatori R, de Souza Araújo AA, Neto RFS, Bartke A, Batista VO, Schneider A, Villar-Gouy KR, Masternak MM, Leal ÂC, Santos LB, Oliveira CRP, Santos EG, Oliveira Simões DA, de Santana Silva B, Aguiar-Oliveira MH. Skin assessment in congenital untreated isolated GH deficiency. Endocrine. 2024 May 4. doi: 10.1007/s12020-024-03840-1. Epub ahead of print. PMID: 38703329

2) Barros-Oliveira CS, Salvatori R, Dos Santos JSS, Santos PFC, Oliveira-Santos AA, Marinho CG, Santos EG, Leal ÂCGB, Campos VC, Damascena NP, Oliveira CRP, Aguiar-Oliveira MH. Sweat and vitamin D status in congenital, lifetime, untreated GH deficiency. Endocrine. 2019 Sep;65(3):710-713. doi: 10.1007/s12020-019-01998-7. Epub 2019 Jul 10. PMID: 31292841.

3)Marinho CG, Mermejo LM, Salvatori R, Assirati JA Junior, Oliveira CRP, Santos EG, Leal ÂCGB, Barros-Oliveira CS, Damascena NP, Lima CA, Farias CT, Moreira AC, Aguiar-Oliveira MH. Occurrence of neoplasms in individuals with congenital, severe GH deficiency from the Itabaianinha kindred. Growth Horm IGF Res. 2018 Aug;41:71-74. doi: 10.1016/j.ghir.2018.03.004. Epub 2018 Mar 12. PMID: 29571594.

1. Saccon TD, Schneider A, Marinho CG, Nunes ADC, Noureddine S, Dhahbi J, Nunez Lopez YO, LeMunyan G, Salvatori R, Oliveira CRP, Oliveira-Santos AA, Musi N, Bartke A, Aguiar-Oliveira MH, Masternak MM. Circulating microRNA profile in humans and mice with congenital GH deficiency. Aging Cell. 2021 Jul;20(7):e13420. doi: 10.1111/acel.13420. Epub 2021 Jun 12. PMID: 34118183; PMCID: PMC8282278.

Minor points:

1)The article is extremely well-written, but some sentences are repeated apparently more than necessary. Please verify this.

2) I will not write that “skin covers around 8% of the human body”, which gives the idea that the majority of the human body is not covered by skin .Instead, I would write that it accounts for  8 to 15%  of the adult human's total body weight.