MODELING SKIN AGING ON A CHIP

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Curriculum: Ingegneria dei Materiali e delle Strutture

Skin aging has always raised a lot of interest from a research point of view, as skin represents one of the most important barriers in human body. Aging leads to a change in the morphology of the skin as well as a decay in its mechanical and structural properties. Finally, this results in a loss of functionality, leading to impaired repairing capability and thus making people prone to different pathological conditions. A deep understanding of the relationships between environmental or endogenous stressors and skin dysfunctionalities represents an urgent need.

There are two different types of aging, namely chronological (or intrinsic) and extrinsic aging. The former is an inevitable consequence of time, while the latter is due to external factors such as UV exposure, pollution, smoke, and dietary habits.

Advanced glycation end-products (AGEs) are a result of non-enzymatic glycation of the extracellular matrix (ECM) proteins occurring after exposure to sugars. As this process occurs rather slowly, it mainly affects proteins with a low turnover, such as collagen. Moreover, AGEs are related to a series of pathological aging-related complications such as diabetes, cardiovascular diseases, Alzheimer's disease and Parkinson's disease. Despite the great concern about long-term effects of AGEs, the mechanisms underlying their formation and action still remain largely unknown.

Apart from the changes in the structure and organization of the ECM, AGEs also affect cellular behavior, as it has been demonstrated the onset of inflammatory responses upon exposure of cell cultures to glycation products [1]. For this reason, a thorough understanding of the effects of AGEs on both ECM and cells is needed in order to better direct future research on possible therapies to ameliorate this harmful condition.

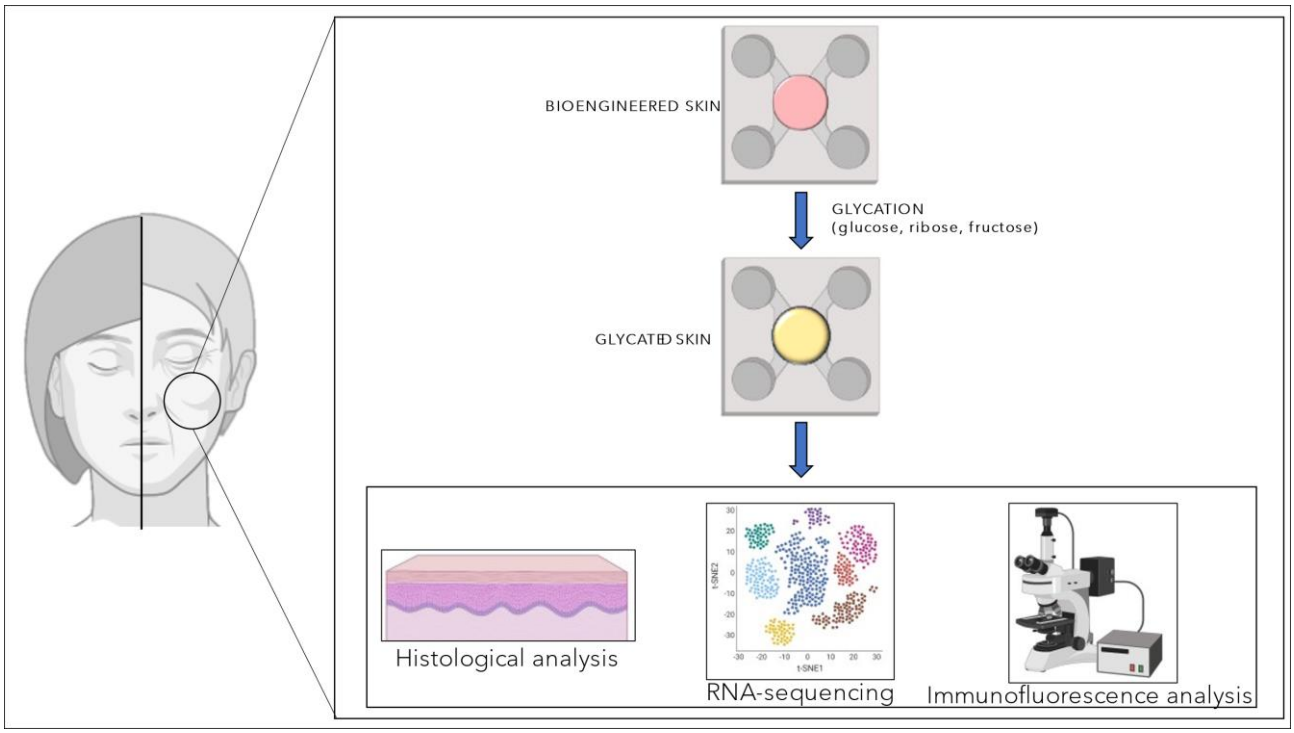
The aim of this PhD project is to investigate the effects of AGEs on the repair mechanisms of the cell once exposed or surrounded by a glycated environment. Indeed, previous studies have shown that cells possess many detoxification systems to counteract the accumulation of glycation products, such as the glyoxalase system. However, during aging or under hyperglycemic diets, the proteolytic activity of these systems become insufficient, thus leading to an accumulation of AGEs.

During the first phase of the project, decellularized bioengineered skins will be glycated to assess the morphological and histological changes occurring at the ECM level during AGEs accumulation [2]. Based on the current literature, protein glycation leads to a masking of fundamental binding sites for collagen attachment to other components of the ECM, such as proteoglycans [3]. This could in turn affect the organization of water molecules, which are fundamental to provide a suitable framework for ECM sustainment and turgidity, with subsequent formation of wrinkles, typical sign of aged skin.

Subsequently, changes in cell transcriptome will be used to highlight genes and pathways that are differentially expressed, hopefully providing an insight into the causes hindering the repair. AGEs can accumulate either intracellularly or extracellularly, thus impacting on the physiological transcriptional activity of the cells [4]. The sequencing techniques are nowadays widespread for analysis at cell-scale level. Not only do they provide a clear and unique fingerprint of the cells at the specific time of the sequencing, but they can also be used to identify novel biomarkers that help predict the time evolution of the pathology.

In conclusion, this PhD aims at shedding light on the unknown mechanisms underlying the formation of advanced glycation end-products, as well as their effect on long-term capacity of the cell to repair the surrounding matrix. The use of a bioengineered *in vitro* skin that can faithfully replicate many of the cellular and molecular dynamics observed *in vivo* provides the ideal platform to mimic and study the onset and the

effects of AGEs. This could represent a decisive step forward towards their amelioration and subsequent improvement of people's quality of life.



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