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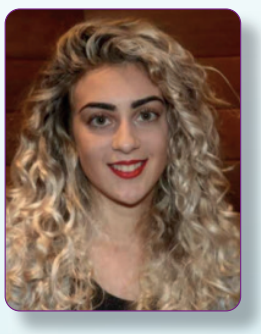

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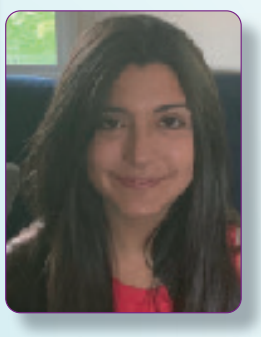

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Transcriptional reprogramming of skeletal muscle stem cells by the niche environment

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Adult stem cells are indispensable for tissue regeneration, but their function declines with age. The niche environment in which the stem cells reside plays a critical role in their function. However, quantification of the niche effect on stem cell function is lacking.

Using muscle stem cells (MuSC) as a model, we show that aging leads to a significant transcriptomic shift in their subpopulations accompanied by locus-specific gain and loss of chromatin accessibility and DNA methylation.

By combining in vivo MuSC transplantation and computational methods, we show that the expression of approximately half of all age-altered genes in MuSCs from aged male mice can be restored by exposure to a young niche environment. While there is a correlation between gene reversibility and epigenetic alterations, restoration of gene expression occurs primarily at the level of transcription. The stem cell niche environment therefore represents an important therapeutic target to enhance tissue regeneration in aging.

In summary, our studies highlight the importance of the muscle stem cell niche environment as a critical regulator of MuSC gene expression. The plasticity of the MuSC transcriptome suggests that modulating the niche environment can be a powerful tool to restore stem cell-mediated endogenous muscle regeneration in aging. Consequently, as opposed to focusing solely on MuSCs themselves to mitigate the effects of aging on MuSCs, bioengineering of the niche in its entirety may be a viable therapeutic option. Our findings also have important implications for preventative therapies, suggesting that potential treatments targeted to the niche would be most effective if administered prior to both the initiation of age-related changes in population dynamics and the onset of alterations in the chromatin state.

Further research is required to identify specific signatures that confer plasticity in MuSC gene expression in response to the niche. Furthermore, 3D mapping of genome architecture, using Hi-C or a related technique, would be required to establish a causal relationship between gene reversibility and changes in chromatin state.

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