2025 NEW YORK REGIONAL SOCIETY OF PLASTIC SURGEONS ANNUAL RESIDENTS' NIGHT RESEARCH COMPETITION

MONDAY, MARCH 10, 2025
NEW YORK ACADEMY OF MEDICINE

ABSTRACT SUBMISSION TITLE: *B4 - Neurotransmitter signaling specifies sweat gland stem cell fate through intracellular calcium regulation*

Additional Author(s):
Jie Tong, Meng Ju Lin, Axel Concepcion, Satvik Mareedu, Gopal Babu, Stefan Feske, and Catherine P. Lu

Abstract Presenting Author:
Juliana Remark, MD

Plastic Surgery Residency Training Program:
NYU Grossman School of Medicine

Abstract Text:

PURPOSE:

Autonomic nerves are essential for all vital physiologic functions of human body. The parasympathetic and sympathetic neurotransmitters (NT), acetylcholine and norepinephrine respectively, engage their corresponding receptors on target organs to regulate their functions, such as heartbeat, blood pressure, muscle movements, digestion, and glandular secretion. It is known that NT signals from these autonomic nerves not only initiate rapid and transient responses in the mature target organs, but may also influence their morphogenesis and regeneration. Sweating, crucial for human thermoregulation and water balance, relies entirely on the neuronal stimuli. The sympathetic nerves innervating sweat glands were classically described as one of the unique cases that undergo a "neurotransmitter switch" from initially releasing sympathetic norepinephrine (NE) to parasympathetic acetylcholine (ACh) during development. In this work, we sought to understand the molecular mechanisms by which neural signals impact sweat gland development.

METHODS:

Through denervation and knocking out specific NT receptor expression during sweat gland development, we examined the role of NTs in sweat gland development through fluorescence-activated cell sorting analysis, whole-mount imaging, calcium imaging, cell culture, and single-cell RNA/ATAC sequencing,.

RESULTS:

In this work, we demonstrated that ductal cells express the Adrb2 receptor and respond to NE, while the glandular cells express the Chrm3 receptor and respond to ACh. The sequence of the neurotransmitter switch (NE then ACh) correlates with the appearance of ductal cells (Adrb2+) and later myoepithelial cells (Chrm3+) during morphogenesis, and we showed that ductal and glandular development is defective in the absence of the respective receptors. We found that without neuronal signals during development, the basal cells switch to exhibit suprabasal (luminal) cell features. Sarcolipin (SLN), a key regulator of sarcoendoplasmic reticulum (SR) Ca2+-ATPase (SERCA) expression is significantly down-regulated in the sweat gland myoepithelial cells upon denervation. Loss of SLN in sweat gland myoepithelial cells leads to decreased intracellular Ca2+ over time in response to ACh stimulation, as well as upregulation of luminal cell features. In cell culture experiments, we showed that contrary to the paradigm that elevation of Ca2+ promote epidermal differentiation, specification of the glandular myoepithelial (basal) cells requires high Ca2+ while lowering Ca2+ level promotes luminal (suprabasal) cell fate.

CONCLUSIONS:

Our work highlights that neuronal signals not only act transiently for mature sweat glands to function, but also exert long-term impact on glandular stem cell specification through regulating intracellular Ca2+ dynamics.