“Neuro-Vascularized Skin Organoids”: Novel Exploratory Research Tools in Leprosy

Research on dermatological diseases is limited by the availability of rigorous models that can recapitulate the complexity of native skin. Murine models that are currently employed to study dynamics of skin development and homeostasis fail to mimic human biology, and the available human skin equivalent systems are limited by the absence of hair follicles, dermal fat cells, and sensory neurons.\(^1\) Currently, the management of local and full-thickness skin defects using stem cell therapy stays a considerable clinical challenge due to inefficient skin regeneration protocols. The immense need for refined models of human skin for research as well as diagnostic purposes has encouraged the development of in vitro skin stem cell regeneration models and organoids that can serve as a source of cells for skin reconstruction and propel studies of human skin development, disease modeling, drug testing, and cell/gene therapies. Skin organoids are the most valuable tools to investigate the developmental biology of skin and cross-talk between broad skin cells including the immune and non-immune sub-populations.\(^2\) With the advancement in genetics, imaging, and high-throughput technologies, there has been a progressive trend towards understanding the relationship between resident skin stem cells and their interaction with the immediate niche, which maintains the overall health and integrity of the skin. Any pathological insult, if not rescued by the adult stem cell populations of the skin, can result in dermatological diseases that can involve/affect diverse skin cells including the ectodermal derivatives (epidermis), mesenchymal derivatives (dermis, hypodermis, and mesodermal connective tissue), resident immune and vascular cells, sensory nerve endings, and neural crest-derived Schwann cells and melanocytes.

The establishment of novel platforms involving the generation of superior neuro-vascularized skin organoids marked by co-development of pericytes, endothelial cells, neurons, melanocytes, Schwann cells, and hematopoietic stem cells or immune cells could facilitate the investigation of infectious inflammatory skin diseases such as erythema nodosum leprosum (ENL)/type 2 leprosy reactions (T2R). Further, patient-derived skin organoids could offer room for understanding patient heterogeneity that may allow for personalized therapies for the treatment of diverse skin diseases. Improved skin organoids, therefore, hold great potential to feed-forward exploratory research toward investigating complex nerve sensation and microbiome-skin interactions, dermatological viral–bacterial co-infections, and high-throughput drug screening, thereby massively advancing basic and clinical research. The recent work by Lee et al.\(^3\) has demonstrated methods to generate skin organoid models from pluripotent stem cells.\(^4\)

More than 150 years after being identified as a human pathogen, Mycobacterium leprae has defied ex-vivo cultivation. Numerous attempts have been made to cultivate the bacteria ex-vivo on axenic culture media as well as in cell culture; however, fastidious growth requirements have led to repeated failure in culture attempts. This had posed major limitations to gaining deeper mechanistic insights into the pathophysiology of leprosy, especially leprosy reactions including ENL. Animal models including long-nosed southern nine-banded armadillo (Dasypus novemcinctus) and mouse footpad (Mus

Keshav Sharma, Seema Chhabra, Maryada Sharma\(^1\)

Departments of Immunopathology and \(^1\)Otolaryngology and Head and Neck Surgery, Postgraduate Institute of Medical Education and Research, Sector 12, Chandigarh, India

Address for correspondence:
Dr. Maryada Sharma,
Department of Otolaryngology and Head and Neck Surgery,
Postgraduate Institute of Medical Education and Research, Sector 12,
Chandigarh - 160 012, India.
E-mail: maryada24@yahoo.com, sharma.maryada@pgimer.edu.in
Dr. Seema Chhabra,
Department of Immunopathology, Postgraduate Institute of Medical Education and Research,
Chandigarh - 160 012, India.
E-mail: drseemachhabra@gmail.com

How to cite this article: Sharma K, Chhabra S, Sharma M. “Neuro-vascularized skin organoids”: Novel exploratory research tools in leprosy. Indian Dermatol Online J 2022;13:388-9.
Received: 02-Dec-2021. Revised: 24-Jan-2022. Accepted: 25-Jan-2022. Published: 05-May-2022.
Sharma, et al.: Novel neuro-vascularized skin organoids in ENL

Musculus) models- the “gold standard animal model” for leprosy research as well as in vitro (human and mouse) leprosy granuloma models involving M. leprae “infection” have been discovered and established over time. None of these models display the full clinical manifestations of the leprosy spectrum including nerve infection and type 1/ type 2 leprosy reactions that are seen in humans. This has been a critical deterrent for investigative research into these serious life-threatening phenomena associated with long-term incapacitation seen in humans. There is a critical need for validated in vitro models of leprosy reactions to use as an exploratory research tool for investigating molecular and cellular players underlying ENL-associated multi-system inflammation.

It is intriguing to leverage this skin organoid model towards the establishment of the novel in vitro M. leprae infected human skin organoids-leprosy granuloma model for studying leprosy, especially reactions. In vitro models consisting of novel vascularized and innervated (Schwann cell myelinated) skin organoids infected with M. leprae and co-cultured with autologous peripheral immune cells can help elucidate the pathophysiology of granuloma formation and immune reshaping underlying ENL. Building and establishing holistic skin organoids by coaxing ectodermal patterning into epidermal and non-epidermal co-emerging lineage derivative, neural crest cells that have the potential to give rise to mesenchymal derivatives (dermis), and Schwann cells (the preferred incubating sites of M. leprae) seems quite promising. A successful infection, survival, and (propagation?) can have path-breaking implications in establishing tractable in vitro personalized ENL models that may help understand the pathophysiology of the disease, develop personalized therapy, and facilitate overcoming the inherent roadblocks and limitations in current leprosy therapeutics.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References
1. Engevik KA, Matthis AL, Montrose MH, Aihara E. Organoids as a model to study infectious disease. Methods MolBiol 2018;1734:71-81.
2. Wang X, Wang S, Guo B, Su Y, Tan Z, Changet M, et al. Human primary epidermal organoids enable modeling of dermatophyte infections. Cell Death Dis 2021;12:35.
3. Lee J, Koehler KR. Skin organoids: A new human model for developmental and translational research. ExpDermatol 2021;30:613-20.
4. Lee J, Rabbani CC, Gao H, Steinhart MR, Woodruff BM, Pfum ZE, et al. Hair bearing human skin generated entirely from pluripotent stem cells. Nature 2020;582:399-404.
5. Muppirala AN, Limbach LE, Bradford EF, Petersen SC. Schwann cell development: From neural crest to myelin sheath. Wiley Interdiscip Rev DevBiol 2021;10:e398.