UNIVERSITE BIOLOGIE BRETAGNE SANTE LOIRE

Year 20 /20

THESIS TOPIC

Subject N° (to be completed by the ED):	**FUNDING:** ☒ **Requested** ☐ **Acquired**	**Funding origin: CDE**
Thesis title: **Study of epidermal innervation and TRPV1 in psoriasis**		3 keywords: Psoriasis Cutaneous innervation TRPV1
Unit / team: **EA4685**		
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Socio-economic and scientific context (approximately 10 lines):
The maintenance of skin homeostasis relies on a finely tuned equilibrium of well-regulated interactions between its different components Including a strong involvement of the peripheral nervous system. Dysregulation of this balance contributes to the pathogenesis of inflammatory skin diseases such as psoriasis, which affects 1-3% of the French population. Although substantial advances have been made on elucidating the role of immune-driven inflammation in psoriasis, **the regulation of inflammation by peripheral nerves was scarcely investigated and remains unclear or contradictory**.
Widely expressed in skin sensory nerve endings, transient receptor potential vanilloid receptor subtype 1 (**TRPV1**) has a prominent role in pain sensation and inflammation, mainly via the local release of several neuropeptides. Although the mechanisms by which the inflammatory mediators in damaged tissues sensitize TRPV1 have received considerable attention, the role of TRPV1 in psoriasis has been seldom addressed. Few studies reported that the ablation of sensory nerves expressing TRPV1 reduces psoriasiform skin inflammation/pattern, thus demonstrating that these neurons **contribute to the inflammation in psoriasis**. **But TRPV1 expression is not restricted to neuronal cells.** It is also expressed by epidermal keratinocytes and endothelial cells on cutaneous microvessels associated with multiple cellular interaction and regulation. Hence, the role of vascular or epidermal TRPV1 in inflammation associated to psoriasis has not been described yet.

Working hypothesis and aims (approximately 8 lines):
We thus hypothesize that, in addition to the participation of the nervous system and neuronal TRPV1, TRPV1 expressed by non-neuronal cells could also be involved in the inflammation process in psoriasis. 1) Is epidermal innervation modified in psoriatic condition? 2) Does the neural system participate and how in the regulation of psoriasis 3) Is TRPV1 expression regulated between normal and in psoriatic conditions (both *in vivo* and *in vitro*, at the organ and the cellular levels)? 4) Does TRPV1 activation modulate the inflammatory response *in vitro*? 5) Is TRPV1 necessary for the development of psoriasis lesions (for each cellular type keratinocytes, neurones, endothelial cells *in vitro* and *in vivo*)?

Main milestones of the thesis (approximately 12 lines):
The project will be divided into two main axes and will require the use of several psoriatic in vitro and in vivo models.
Axis 1: **Characterization of the innervation and study of the expression of TRPV1 in normal and psoriatic skin**. The characteristics of the epidermal innervation (structure, number and length of nerve fibers, synaptic contacts) as well as the expression of TRPV1 in the 3 skin cellular types (keratinocytes, neurons, endothelial cells) will be analyzed by immunohistochemistry using skin biopsies obtained from a mouse model mimicking psoriasis (using imiquimod, IMQ, which induces a psoriasis phenotype) and from psoriatic patient. These results will be completed by an analysis of the expression of TRPV1 *in situ* (RNAscope on tissue sections) and on whole sample (qPCR) of the skin of patients and of the skin and the sensory neurons of treated (IMQ)/control mice.
Axis 2: **Participation of TRPV1 expressed by neurons, keratinocytes and endothelial cells in psoriasis-associated inflammation**
Axis 2a A first approach will be carried out through the study of TRPV1 sensitization on cultures of human neurons, keratinocytes or endothelial cells as well as a reinnervated skin explant model incubated with a cocktail of cytokines (TNF, IL17A, IL22, Oncostatin M, IL1a) inducing a "psoriasis phenotype" *in vitro*. In practice, the cells will be subjected to the cocktail in the presence or absence of capsaicin, a TRPV1 agonist, then the modulation of expression of the pro-inflammatory cytokines markers of psoriasis will be analyzed.
Axis 2b The second approach will be on the same type of experiment but the TRPV1 agonist will be replaced by antagonists in order to highlight the participation of TRPV1 in the production of po-inflammatory cytokines induced by the cocktail. This approach will be completed by histological analysis of the psoriatic phenotype on skins (already obtained and stored in the laboratory) of TRPV1 KO mice and specific tissue (epidermis, sensory neurons, endothelium) TRPV1 KO mice (in production) with or without Imiquimod.

Scientific and technical skills required by the candidate (2 lines):
Very good knowledge of the skin is required. Practice of cell culture, histology, classical techniques of biochemistry and molecular biology are highly recommended.

3 publications from the team related to the topic (last 5 years):
Keratinocytes Communicate with Sensory Neurons via Synaptic-like Contacts
Talagas M, Lebonvallet N, Leschiera R, Sinquin G, Elies P, Haftek M, Pennec JP, Ressnikoff D, La Padula V, Le Garrec R, L'herondelle K, Mignen O, Le Pottier L, Kerfant N, Reux A, Marcorelles P, Misery L. Ann Neurol. (IF9.03) 2020
Major role for TRPV1 and InsP3R in PAR-2-elicited inflammatory mediator production in differentiated human keratinocytes
Gouin O, L'Hérondelle K, Buscaglia P, Le Gall-Ianotto C, Philippe R, Le Goux N, Mignen O, Buhe V, Leschiera R, Sakka M, Kerfant N, Carré J-L, L Lefeuvre L, Lebonvallet N*, Misery L*.
J Invest Dermatol. 2018 Feb 16.
TRPV1 and TRPA1 in cutaneous neurogenic and chronic inflammation: pro-inflammatory response induced by their activation and their sensitization.
Gouin O, L'Herondelle K, Lebonvallet N, Le Gall-Ianotto C, Sakka M, Buhé V, Plée-Gautier E, Carré JL, Lefeuvre L, Misery L, Le Garrec R.
Protein Cell. 2017 Mar 31

National and international collaborations:
This work is part of a project funded by national agency studying the rule of TRPV1 in inflammation in psoriasis. The main collaborator are Bérengère Fromy (DR CNRS and director of the laboratory LBTI Lyon), and Jean -Claude Lecron (Professor, LITEC Poitiers)