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Ion channels: promising targets in pathologies

by **Christophe Vandier**

As a PhD student I learned electrophysiology (ion channel activity) at the University of Poitiers (France) where Edouard Coraboeuf recorded for the first time intracellular cardiac action potentials, which was the world's first one made with intracellular microelectrodes. With electrophysiology and the patch-clamp technique, the activity of ion channels can be recorded in live cells, which allows a deeper study of ion channels roles and their implication within cell functions.

Ion channels regulate major physiological functions by controlling excitation-response couplings such as excitation-contraction/secretion couplings of excitable cells and their deregulation or mutations lead to pathologies called channelopathies. More recently, their roles have been described in cancer and it is now established that they control most of the important cell biological functions of tumor development such as proliferation, migration/invasion and resistance to treatments. Among ion channels, potassium channels (K^+ channels) are the most represented and diversified family. The control of biological functions of cancer cells by K^+ channels are increasingly documented and it is generally accepted that K^+ channels control biological functions by promoting tumorigenicity and tumor aggressiveness. Additionally, their expression is associated with poor survival.

Among K^+ channels, the calcium activated potassium channels (SKCa) family, are prime targets for the development of cancer therapies[1]**.** Our research revealed that **SKCa channels** and SK3 channel specifically, play a key role in controlling the plasma membrane potential by inducing hyperpolarization, which ultimately promotes cell migration and invasion[2]. The role of SK3 channel in breast, melanoma, prostate, colon, and uterine/ovary cancer cell migration/invasion to promote bone cancer metastasis has already been well described[3-6]. Recent data demonstrates that another SKCa family member, the SK2 channel, contributes to migration/invasion of pancreatic cancer cells and drives pancreatic cancer cells aggressiveness[7]. In addition, inhibition of SK2 currents reduce the proliferation of melanoma cells under hypoxia according to an unsolved mechanism[8]. SK1 is the SKCa channel less studied due to lack of relevant antibodies and inhibitors, nevertheless we have recently found that *KCNN1* mRNA (coding for SK1) is overexpressed in Ewing sarcoma, promoting cell proliferation and being associated with poor survival[9] and additionally, it is also upregulated in breast cancer, promoting proliferation and migration processes[10].

These data support the idea that SKCa channels may be a major target for the development of anticancer therapies and therefore there is an urgent need to develop specific SKCa channels blockers.

The neurotoxin related peptide Apamin, was described some decades ago as a SKCa channel blocker in the neuron system, but unfortunately the absence of target specificity was translated into highly toxicity. Something similar was found with a synthetic alkyl ether-lipid that has promising anti-migratory effects on cancer cells, via SK3 inhibition: edelfosine[11]. However, it was observed[12] in clinical tests that edelfosine as an independent drug is poorly suitable for treatment of tumors because of its high hemolytic activity.
Based on all these evidences, with my team we have created a platform for drug screening based on an exhaustive evaluation of toxicity on normal cells, patch clamp for the measurement of channel activity, and migration in cancer cell lines. Dozens of compound analysis led the development of **Ohmline** as the first SKCa channel inhibitor that can discriminate SK1/3 from SK2, showing highest inhibitory effect on SK3 with no toxicity associated. For the first time we are able to decrease the channel activity without affecting normal cells.

But as you may anticipate, ion channels are not only crucial targets for new cancer therapies development, but also for another biological processes where these channels play a crucial role, such as for bacterial membrane stability. K^+ channels are essential for bacterial cellular homeostasis and communication (quorum sensing/biofilms), maintaining a critical role in membrane potential modulation, intercellular and interspecies communication, and memory formation. Membrane potential is then essential for sub-second functions such as mobility and cellular respiration, but also important for minute-to-hour time scale processes such as cell division and communication between cells. Targeting K^+ channels is therefore key to disrupt bacteria survival, interaction, adaptation and communication in a variety of environmental conditions. Our new advances in this regard will change the way antibiotics are used and will open new treatments avenues in the fight against antibiotic resistance.

As a co-founder and team member of Lifesome Therapeutics, I feel enthusiastic and honoured to contribute to the development of the first therapeutic nanocarrier in the market made of an ether-single lipid compound, Ohmline, that is a specific blocker of K^+ channels and specifically SK3 channels. This active nanocarrier not only presents therapeutic activity itself but can also carry various compounds such as anticancer/antibiotic drugs thus leading to promising advancements in oncotherapy, antibiotic resistance and many other therapeutic areas.

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About the author

Christophe VANDIER is Professor of Physiology at the University of Tours (France) and Director of the Niche-Nutrition-Cancer & Oxidative metabolism Laboratory (joint research Unit between the University of Tours and INSERM, UMR 1069). After working in the field of vascular physiology for 10 years, Christophe Vandier joined the Niche-Nutrition-Cancer & Oxidative metabolism laboratory of the University of Tours in 2004 to develop research aimed at studying the role of ion channels as molecular actors of nutritional lipids in cancer. At the same time, Christophe Vandier participated in the development of the "Ion Channels and Cancer" network of the Cancéropôle Grand Ouest (as coordinator), which has now become the "marine molecules, metabolism and cancer" network that he co-coordinates. Christophe Vandier has a h-index of 31 with a total of 86 publications, 5 patents and is co-founder of the start-up Lifesome Therapeutics.