SK3 Gene Polymorphism Is Associated with Taxane Neurotoxicity and Cell Calcium Homeostasis

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Abstract

Purpose: Taxane-induced peripheral neuropathy is a common side effect induced by anticaner agents, and no drug capable of preventing its occurrence or ameliorating its long-term course has been identified. The physiology of taxane neuropathy is not clear, and diverse mechanisms have been suggested, with ion channels regulating Ca2+ homeostasis appearing good candidates. The calcium-activated potassium channel SK3 is encoded by the KCNN3 gene, which is characterized by a length polymorphism due to variable number of CAG repeats.

Experimental Design: To study the influence of the polymorphism of CAG motif repeat of KCNN3 on the development of taxane-induced neuropathy, we evaluated 176 patients treated with taxanes for breast cancer. In parallel, we measured Ca2+ entry using Fura2-AM dye in HEK cells expressing short versus long CAG alleles of KCNN3.

Results: In the current study, we report that in the presence of docetaxel, Ca2+ entry was significantly increased in cells expressing short versus long CAG alleles of SK3 and that a SK3-lipid blocker inhibits this effect. We found that patients carrying a short KCNN3 allele exhibited significantly increased incidence of taxane neuropathy compared with those carrying longer alleles.

Conclusions: The clinical implication of these findings is that KCNN3 polymorphism may increase patient susceptibility to taxane neurotoxicity and that the use of SK3 blockers during taxanes’ administration may represent an interesting approach for the prevention of this neurotoxicity.

Introduction

Taxane-induced peripheral neuropathy is a common side effect induced by paclitaxel and docetaxel (1, 2). In clinical practice, the most common feature of taxanes neurotoxicity is a predominant sensory distal neuropathy with paresthesia, numbness, tingling, and shooting pains (2). These side effects may seriously compromise the quality-of-life and this effect may be mediated by the activation of the Ca2+-activated proteases calpains (4). Because Ca2+ concentration is regulated by ion channels, another hypothesis is that taxanes neurotoxicity may involve ion channels regulating Ca2+ homeostasis. Paclitaxel (Taxotére®) was also found to activate the transient receptor potential channel (TRP4; ref. 5), and paclitaxel can activate the voltage gated Ca2+ channel CaV3.2 (6). Docetaxel was also found to modulate the activity of K+ channels known to regulate membrane potential and therefore Ca2+ entry (7).

Interestingly, the SK3 potassium channel has been found to be associated with oxaliplatin neurotoxicity (8), and we reported a pivotal role of this channel in the regulation of Ca2+ homeostasis and Ca2+-activated proteases calpains (9, 10). SK3 channel belongs to Ca2+-activated K+ channel family (KCa). KCa channels can be divided into three subfamilies: large or big conductance KCa (BKCa), intermediate conductance KCa (IKCa), and small conductance KCa (SKCa). SKCa channels are voltage insensitive and are activated by low concentrations of cytosolic Ca2+. There are three isoforms of SKCa, alpha subunits, named SK1, SK2, and SK3, which associate to form homo- or heterotetramers (11).
Contrary to SK1, SK2, and SK3 channels are not restricted to neuronal tissues (12), and SK3 channels were found to be expressed in dorsal root ganglion neurons, where they are activated after sensory stimulation and act to control sensory input into the spinal cord (13).

In excitable cells such as neurons, the activation of SK3 channels by low Ca\(^{2+}\) concentrations, results in hyperpolarization of the plasma membrane and changes in cellular excitability. In neurons, SK3 channel activation also counteracts further increases in cytosolic Ca\(^{2+}\), thereby regulating its concentration and controlling neuronal firing properties and neurotransmitter release (14). The KCNN3 gene is highly polymorphic with the presence of a variable number of CAG triplet repeats in the region encoding the N-terminal domain. It was demonstrated that cells carrying alleles with an elevated number of CAG repeats (i.e., long length alleles containing 24 CAG repeats compared with 18 or 11) display reduced SK3 channel activity with a reduction of the amplitude of SK3 current and a left-shift of the inward rectification to reduced membrane potential values (15). Previous studies have demonstrated that SK3 channel regulates neuronal activity through the regulation of after hyperpolarization (16), and the length of the CAG repeat could generate different after hyperpolarization, thereby modulating neuronal excitability.

Interestingly, a relationship between KCNN3 polymorphism and the severity of peripheral neuropathy following oxaliplatin treatment has been identified in colon cancer, with patients that carry short CAG repeats (14–16) experiencing more severe neuropathy (8).

In the current study, we tested the effect of docetaxel on the regulation of cytosolic Ca\(^{2+}\) concentration that is controlled by the SK3 channel activity in cells carrying long and short CAG repeats in KCNN3. To study the influence of the polymorphism of CAG motif repeat of KCNN3 on the development of taxane-induced neuropathy, we evaluated patients treated with taxanes for breast cancer.

Materials and Methods

**In vitro analysis**

HEK293 cells were maintained in DMEM, supplemented with 10% (v:v) FBS (Lonza) and were grown in a humidified atmosphere at 37°C (95% air, 5% CO\(_2\)). HEK293 cells, expressing short (11 CAG repetitions) or long (24 CAG repetitions), SK3 channel isoforms were kindly provided by L. Pardo (Max Planck Institute of Experimental Medicine, Göttingen, Germany). Genetic analysis of KCNN3 polymorphism was controlled as described below. Three days after thawing and 15 days later, cells were monitored for Mycoplasma contamination using the MycoAlert Mycoplasma Detection Kit (Lonza) and were replaced after one month in culture. Number passages were limited to 13 after stable transfection with SK3 channel isoforms.

**Drugs and solutions**

Drugs were added to the physiologic saline solution (PSS) or culture media at the concentrations indicated in figure legends. All drugs were purchased from Sigma-Aldrich.

The PSS or "2Ca" solution had the following composition (in mmol/L): NaCl 140, MgCl\(_2\) 1, KCl 4, CaCl\(_2\) 2, 2-glucose 11.1, and HEPES 10, adjusted to pH 7.4 with NaOH. The Ca\(^{2+}\)-free solution or "0 Ca" is a PSS solution without CaCl\(_2\) and with 1 mmol/L EGTA.

**Ca\(^{2+}\) entry measurements**

The effect of docetaxel on cytosolic Ca\(^{2+}\) was evaluated and compared using HEK293 cells that expressed different KCNN3 CAG repeat length [SK3(CAG)\(_{24}\) and SK3(CAG)\(_{11}\)]. Time-lapse Ca\(^{2+}\) cytosolic measurements were performed using the FlexStation III fluorometer (Molecular Devices). HEK293 cells were seeded on 96-well flat clear-bottom black microplates (3603, Corning) at a density of 3 \times 10\(^4\) cells/well. HEK293 cells were grown on fibronectin-coated microplates. One day after seeding, HEK293 cells were incubated with 4 μmol/L Fura-2/AM in culture medium for 35 minutes at 37°C protected from light. Afterward, the cells were gently washed three times with HEPES-buffered saline (140 mmol/L NaCl, 1.13 mmol/L MgCl\(_2\), 4.7 mmol/L KCl, 2 mmol/L CaCl\(_2\), 10 mmol/L 2-glucose, and 10 mmol/L HEPES, pH 7.4) and left for 5 minutes at room temperature and protected from light. Data acquisition was performed using SoftMax pro software. Fura-2-loaded cells were alternately illuminated with 340 and 380 nm. Fluorescence emission was collected at 510 nm. Figures showing Ca\(^{2+}\) traces show averages from several well per condition and are representative of several independent recordings.

In HEK293 cells, Ca\(^{2+}\) homeostasis is regulated by store-operated channels that mediate store-operated Ca\(^{2+}\) entry (SOCE). An easy method to induce SOCE is to deplete Ca\(^{2+}\) from the endoplasmic reticulum using thapsigargin (a SERCAs inhibitor). Immediately after the loading, cells were washed in PSS with Ca\(^{2+}\)-free solution and treated with thapsigargin (2 μmol/L; T7458, Life Technologies): After intracellular store depletion, 2 mmol/L CaCl\(_2\) was injected (2 Ca solution). Fluorescence emission was measured at 510 nm with an excitation light at 340 and 380 nm (FlexStation 3).

Clinical study

**Patients and protocol.** This study was conducted between November 2012 and May 2014 in a population of women treated for breast cancer using taxanes at the University Hospital of Tours (Tours, France). The study was approved by the Ethics committee of the hospital, was conducted in accordance with recognized ethical guidelines, and written informed consent was obtained.
from all patients. Patients with preexisting neuropathy or who had received chemotherapy known to induce neuropathy (vinca-alkaloids, platinum, eribulin mesylate, or bortezomib) were not eligible. Patients had never received taxanes before this study. Included patients received either 100 mg/m\(^2\) docetaxel via intra-venous infusion on day 1 of a 21-day cycle or 60 mg/m\(^2\) paclitaxel as a weekly intravenous infusion every 21 or 28 days. The neoadjuvant and the adjuvant protocols lasted 4 and 3 cycles, respectively. The duration of the metastatic protocol depended on each patient tolerance.

**Neurologic study.** Depending on patient history and their physical examination, neuropathies were evaluated using the NCI Common Terminology Criteria for Adverse Events (NCI-CTCAE). The grade of neuropathy was based on the duration and intensity of symptoms (grade 0: no symptoms; grade 1: paresthesia and/or decreased osteotendinous reflexes; grade 2: severe paresthesia and/or weak muscle weakness; grade 3: intolerable paresthesia and/or significant motor loss and grade 4: paralysis). The time, intensity, and doses of taxanes were recorded at the emergence of neuropathy, and the same data were collected if the patient demonstrated an increased grade during chemotherapy. During the follow-up, the continuation of the chemotherapy was recorded.

**Genetic analysis of KCNN3 polymorphism.** Genomic DNA was extracted from peripheral blood leukocytes using a FlexiGene DNA Kit according to the manufacturer’s instructions (QIAGEN). The DNA region containing the repeated trinucleotide sequence (in exon 1) was amplified by the fluorescent PCR method with a DNA thermal cycler, using the sense primer 5'-CAGCAGCCCTCGC- TGGGACCCTCGC and the antisense 5'-6-FAM GGAGTTGGGC- GAGCTGAGACAG. PCR was carried out in a total volume of 50 µL containing 100 ng of genomic DNA, 1 µL of each primer (10 µmol/L), 5 µL Accuprime PCR buffer II (10×), and 1 µL of Taq polymerase (Invitrogen). The amplification protocol was as follows: denaturation at 95°C for 4 minutes, 22 thermocycling cycles (annealing at 55°C for 60 seconds and primer extension at 72°C for 30 seconds), and a final extension at 72°C for 10 minutes. The length of the PCR product generated depended on the number of CAG repeats. PCR products were separated by size using capillary electrophoresis on an Applied 3130XL automated DNA capillary sequencer (Applied Biosystems). GeneScan 500 ROX Size Standard was used as standard to extrapolate the size of the sample product peaks. Because both the position of the primers used in the PCR and the number of bases amplified that are not CAG repeats are known, it is easy to deduce the number of CAG repeats from the size of fragments obtained by capillary electrophoresis. Furthermore, the sizes of polymorphic amplicons should differ by a multiple of 3 units from each other. Using the reference sequence of KCNN3 gene in the Ensembl gene browser (https://www.ensembl.org), the expected fragment size of the allele comprising 14 CAG repeats is 121 pb. However, to further validate our method and standardize our allele sizes, we compared it with direct sequencing. The DNA region containing the polymorphism was amplified using the same primers, albeit unlabeled for the antisense one, and the same PCR conditions except for the number of thermocycling cycles that was increased to 45. Electrophoretic Separation of DNA fragments was performed on agarose gels. After cutting the DNA bands out of the agarose gel, the DNA samples were purified and analyzed by Sanger chain termination DNA sequencing. The number of CAG repeats was determined by direct counting of these triplets of bases on electropherograms. The concordance between the two methods was assessed in 12 patients by plotting the number of CAG repeats counted on the electropherograms against the length of the fragments obtained from capillary electrophoresis. Once validated, this latter method was preferred for genotyping of the whole cohort as it is much easier to interpret as compared with electropherograms.

To explore a potential role of the KCNN3 CAG repeat length, we used the sum of both alleles as described previously for schizophrenia (15). We use the median of the sum of CAG repeats distribution to determine each group.

**Results**

**Effect of docetaxel on Ca\(^{2+}\) entry depending on KCNN3 polymorphism**

To determine whether KCNN3 polymorphism was associated with a modulation of calcium metabolism in cells, HEK293 cells carrying SK3(CAG)\(_{24}\) or SK3(CAG)\(_{11}\) were obtained and tested. Figure 1A shows that thapsigargin can induce a transient increase of cytosolic Ca\(^{2+}\) in the absence of external Ca\(^{2+}\) followed by a large increase of cytosolic Ca\(^{2+}\) after addition of external Ca\(^{2+}\) (a.k.a., SOCE). This finding was observed with HEK293-SK3 (CAG)\(_{24}\) and HEK293-SK3(CAG)\(_{11}\). The amplitude of SOCE was not significantly different between HEK293-SK3(CAG)\(_{24}\) and HEK293-SK3(CAG)\(_{11}\) cells under control condition (Fig. 1B). However, in the presence of 10 µmol/L docetaxel, the amplitude of SOCE was significantly increased in HEK293-SK3(CAG)\(_{11}\) compared with HEK293-SK3(CAG)\(_{24}\) cells (Fig. 1B). Interestingly, docetaxel has no significant effect on the amplitude of SOCE in HEK293-SK3(CAG)\(_{24}\) (Fig. 1B). To test whether docetaxel increased the amplitude of SOCE of HEK293-SK3(CAG)\(_{11}\) by increasing the activity of SK3 channel, we tested Ohmline (1-0-hexadecyl-2-O-methyl-sn-glycero-3-lactose) at 300 nmol/L, a lipid inhibitor of the activity of SK3 channel (9), on the amplitude of SOCE recorded in HEK cells. Figure 1C and D shows that Ohmline significantly reduced the amplitude of SOCE recorded in HEK293-SK3(CAG)\(_{11}\) to a level similar to the amplitude of SOCE recorded in the absence of docetaxel (Fig. 1B). As expected, Ohmline has no significant effect on the amplitude of SOCE recorded in HEK293-SK3(CAG)\(_{24}\) cells (Fig. 1D).

**Patients**

A total of 176 patients were enrolled in this study and their characteristics are summarized in Table 1. Among these patients, 3 received both types of taxanes over the course of their treatment. A change of chemotherapy was caused by hematologic or cutaneous toxicity. Median age was 54.2 years. Most of the patients (35.1%) received chemotherapies in an adjuvant setting, and docetaxel was the most frequently used taxane (77.3% of patients).

**Neuropathy**

No patients had any neuropathy prior to the chemotherapy initiation. Among 176 patients, during chemotherapy, 99 patients...
experienced paresthesia (56.2%) and when present, neuropathy was mainly of grade 1 (41.5%, 73 patients). According to the clinical evaluation, neuropathy was absent in 77 patients (G0, 43.7%), mild in 22 patients (G2, 12.5%), and severe in 4 patients (G3, 2.7%). No grade 4 were observed. Figure 2 shows that neuropathies appeared mostly during the first 6 months of treatment and that the likelihood for appearance of neuropathy did not differ between paclitaxel or docetaxel treatments. The mean cumulative dose received by patients when neurotoxicity appeared was 170.4 ± 349.1 mg/m² for paclitaxel and 130.7 ± 149.4 mg/m² for docetaxel.

Genetic findings and neuropathy

Fluorescent capillary electrophoresis provided excellent results with one (homozygous) or two peaks (heterozygous) for each patient, separated by a multiple of 3 units (Fig. 3A). A perfect concordance was obtained between the size of the amplicons

| Table 1. Characteristics of the patients enrolled in the study |
|---------------------------------|-----------------|
|                                | N = 176         |
| Age                            | 54.2 ± 11.5 (30-88) |
| BMI                            | 24.3 ± 4.6 (15.6-37.0) |
| Chemotherapy                   |                 |
| Neoadjuvant                    | 48 (27.3%)     |
| Adjuvant                       | 97 (55.1%)     |
| Metastatic                     | 31 (17.6%)     |
| Taxane                         |                 |
| Paclitaxel                     | 43 (24.4%)     |
| Docetaxel                      | 136 (77.3%)    |
| Histologic type                |                 |
| Ductal                         | 141 (80.1%)    |
| Lobular                        | 20 (11.4%)     |
| Other                          | 15 (8.5%)      |

NOTE: Clinical and histologic features and type of chemotherapy. Other histologic types are mixed (ductal and lobular), mucinoid, and papillar. Three patients received both taxane drugs. Abbreviation: BMI, body mass index.
assessed by fluorescent capillary electrophoresis and the number of CAG repeats obtained by electropherograms analysis in the 12 patients that were analyzed by the two methods (Fig. 3B).

In our cohort, 44 patients (25%) were homozygous for a type of CAG repeats (i.e., carried 2 alleles of the same length) and 135 (75%) were heterozygous. The number of CAG repeats ranged from 13 to 21, with 19 CAG repeats being the most frequent (Fig. 4). The sum of both CAG allele repeats ranged from 26 to 41, with 36–38 being the most frequent and a median around 37 (Fig. 5A). We found a significant difference in neuropathy between patients carrying long forms (sum of CAG repeats ≥ 37) versus short (sum of CAG repeats <37; Fig. 5B). Indeed, a shorter CAG sum was associated with an increased probability of neuropathy (P = 0.036) with 65.9% of patients with short CAG sums experiencing neuropathies as compared with 47.3% of those with long CAG sums [risk ratio (RR) = 1.51; 1.02; 2.3].

To confirm that patients carrying alleles containing short CAG repeats experienced increased neuropathy incidence than patients carrying long CAG repeats, we chose to consider only the homozygous population, that is, patients with the same CAG repeat number for both alleles. Figure 5C shows that CAG repeat numbers in homozygous patients ranged from 13 to 20, with 18–19 CAG repeat being the most frequent. The median of the CAG repeat is 19 corresponding to the median of the CAG repeat sum of 38. As expected, short CAG alleles (repeats <19 CAG) were highly associated with neuropathy incidence as compared with long CAG ones (repeats ≥ 19 CAG; P = 0.016; Fig. 5D). A total of 84.6% of patients carrying two short alleles experienced...
neuropathy compared with 48.4% of patients with two long alleles (RR = 2.5; 1.2; 8.1).

Discussion

We report that patients receiving taxanes during chemotherapy for breast cancer have a different likelihood of developing a peripheral neuropathy according to the CAG polymorphism of KCNN3 encoding the SK3 channel. Patients with short KCNN3 CAG alleles have a significantly higher incidence of taxane neuropathy as compared with patients carrying longer alleles. Consequently, a CAG polymorphism of the SK3 channel is associated with taxane-induced peripheral neurotoxicity.

Taxane-induced peripheral neuropathy is a limiting factor for the use of taxanes such as paclitaxel and docetaxel because they impact patient’s quality-of-life. Indeed, some patients experience invalidating neuropathy, which is sometimes irreversible, or may last years after the end of chemotherapy. The pathophysiology of taxane-induced peripheral neuropathy is not well understood and diverse mechanisms have been proposed.

Figure 4.
Distribution of KCNN3-CAG repeat numbers for each allele in four cohorts of patients receiving taxane chemotherapy for breast cancer. The distribution of KCNN3-GAG repeats numbers was recorded in 176 patients receiving a taxane-based chemotherapy for breast cancer. Although the number of CAG repeats ranged from 10 to 23, 19 CAG repeats was the most frequent allele.

Figure 5.
A and B, Distribution of the sum of KCNN3-CAG repeats for each patient in the cohort and the associated probability of experiencing neuropathy. A, Distribution of the sum of CAG repeats from each allele recorded for the 176 patients receiving a taxane-based chemotherapy for breast cancer. Although the number of CAG repeats ranged from 26 to 41, the median was 37. B, Probability of neuropathy development according to the sum of CAG repeats. A significant difference between patients carrying long and short forms of CAG repeats was observed. C and D, Distribution of CAG repeats in the homozygous population and the associated probability of experiencing neuropathy. C, Distribution of CAG repeats for each patient. Although the number of CAG repeats ranged from 13 to 20, the median was 19. D, Probability of neuropathy development according to CAG repeat numbers. A significant difference between patients carrying long and short forms of CAG repeats was observed.
Interestingly, our results show that in the presence of docetaxel, Ca\(^{2+}\) entry is significantly higher in cells expressing short CAG alleles of SK3 channel than the long forms. Because it was demonstrated that long CAG alleles in the KCNN3 gene lead to a reduction of SK3 channel activity (15), we propose that the increased Ca\(^{2+}\) entry induced by docetaxel is linked to the activity of SK3 channel. Interestingly, Ohmline reduced the amplitude of SOCE that is increased by docetaxel in cells expressing short CAG alleles in the KCNN3 gene to a same level as the amplitude of SOCE recorded in the absence of docetaxel. Because we found that Ohmline is acting in active SK3 channel, (9) this strongly suggests that the increased Ca\(^{2+}\) entry induced by docetaxel is linked to the activity of SK3 channel. This finding is in agreement with the observation that docetaxel and paclitaxel can both activate voltage-independent Ca\(^{2+}\) channel such as transient receptor potential channels TRPV4 (5), TRPA1 (17), and the voltage-gated Ca\(^{2+}\) channel (CaV3.2; ref. 6). The increased Ca\(^{2+}\) entry induced by taxanes may in turn activate Ca\(^{2+}\)-sensitive proteases, leading to the degeneration of peripheral and central branches of dorsal root ganglia axons, as observed previously (3, 4). We have already reported that the SK3 channel, which is expressed in dorsal root ganglion neurons (13), promotes Ca\(^{2+}\) entry and the activity of Ca\(^{2+}\)-activated proteases calpains (9). Our hypothesis is that docetaxel increases the activity of SK3 and/or voltage-independent Ca\(^{2+}\) channel in dorsal root ganglion neurons. This activity could induce cytosolic Ca\(^{2+}\) concentrations that in turn activate SK3 channels. As a result, activation of the SK3 channel may therefore be enhanced in cells expressing short CAG repeat alleles compared with the long forms. Therefore, hyperpolarization of the plasma membrane due to short SK3 channel forms increases the Ca\(^{2+}\) entering force and consequently favors Ca\(^{2+}\) entry. A positive feedback loop between Ca\(^{2+}\) and SK3 channels may ensue, and it may be more efficient in cells expressing short SK3 CAG channels than long forms.

The electrophysiological properties of SK3 channels differ between short and long forms of the SK3 channel. A short CAG repeat number in the KCNN3 gene leads to increased SK3 channel activity (15). However, it is not known how the N-terminus domain of the SK3 channel can interfere with the expression and activity of the channel. In heterozygous population, we do not know the phenotypic effect of different KCNN3 CAG repeat numbers on the SK3 channel activity. Because this complex is formed by the association of four homo or hetero alpha subunits, the most likely association is a heterotetramerization between different CAG repeats lengths. If such an association may be observed in patients, it was not the case in the HEK293 cell lines that are homozygous.

The number of CAG repeats in KCNN3 we have measured in patients is in agreement with their prevalence described among Caucasian populations (8, 15, 18, 19). The increased SK3 channel activity observed for short KCNN3 alleles in patients with breast cancer is associated with a significantly increased incidence of taxane neuropathy compared with patient carrying long alleles. This association was already observed in patients receiving oxaliplatin for colorectal cancer (8). To our knowledge, our study is the first one that combines genetics and in vitro data to demonstrate that SK3 gene polymorphism is associated with taxane neurotoxicity. In the current study, we chose to include all patients with taxane treatment because we did not expect major differences between docetaxel and paclitaxel in term of neuropathy and genetics findings because the two drugs are members of the same pharmacologic family. We found no significant difference in neuropathy incidence between the two drugs, and this finding is in agreement with results showing that patients receiving paclitaxel and docetaxel experienced similar symptoms of taxane-induced peripheral neuropathy (20).

In our study, we found that the CAG polymorphism of KCNN3 is associated with taxane-induced peripheral neurotoxicity. Determination of KCNN3 polymorphism in patients prior to taxane administration may therefore help identify those at risk of developing taxane-induced peripheral neuropathy. For these patients, another type of chemotherapy or schedule of administration could be proposed. Understanding the mechanism of chemotherapy-induced peripheral neuropathy is also important to develop new drugs capable of preventing or treating taxane-induced peripheral neuropathy. Confirmation of the role of the SK3 channel in taxane-induced peripheral neuropathy could lead to the use of inhibitors of the SK3 channel in patients carrying a short polymorphism to prevent or treat these neuropathies. We have already developed synthetic alkylation-ether-lipids, such as Ohmline, that target cell membranes and are specific and nontoxic inhibitors of the SK3 channel (21).

In conclusion, even if there is a need to confirm these observations, this study shows for the first time the presence of a genetic predisposition to develop taxane-induced neurotoxicity, and we identified a mechanism of action that involves the effect of taxanes on SK3-dependent Ca\(^{2+}\) regulation. As a next step, it will be important to determine whether the expression of long and short SK3 channels affects dorsal root ganglion neurons and if so, to test the effect of specific SK3 blockers.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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