

In reply

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Dear editor,

We are sincerely grateful to Dr Park and colleagues for their comment on our article concerning the possible relationship between *acute* oxaliplatin-induced neurotoxicity and SK3 polymorphisms. Any remark on this topic may contribute to improve the knowledge on this complex and serious event.

In our study, we found a significant association between the occurrence of *acute* oxaliplatin neurotoxicity and the presence of a shorter CAG repeat polymorphism of SK3 gene [1]. We did not conclude on the molecular mechanism relating the two events, but only speculated on a possible interference of oxaliplatin with K⁺ channels tetramerization. This fascinating speculation seems supported by a report suggesting the crucial role of the polyglutamine tract of SK3 channel in modulating both tetramer formation and channel function [2]. Taken together, the last observation and our results contribute in generating the hypothesis that we have suggested, which needs validation in a proper experimental setting, as we have clearly specified in our paper.

We agree with Dr Park and colleagues on the existence of several in vitro and in vivo studies suggesting an impairment of voltage-gated Na⁺ channels (VGNaCs) in the pathogenesis of oxaliplatin-induced neurotoxicity [3–6]. As we have also discussed in our paper, these studies showed that oxaliplatin prolongs the duration of nerve relative refrac-

tory period, assuming that this effect is a clear-cut measure of the direct inactivation kinetic of voltage-gated transient Na⁺ channels [3]. However, some other factors might contribute to the nerve refractoriness, such as acid–base balance and Ca²⁺ ion concentration. Interestingly, in vitro studies have also demonstrated that the effect of oxaliplatin on inward sodium current was mimicked by strong calcium ions chelators, suggesting an indirect effect of oxaliplatin on VGNaCs [4]. The same authors also observed that, when neuronal cells were exposed in vitro to oxaliplatin for prolonged interval of times, an important reduction in both depolarizing and post-hyperpolarizing phases occurred, resulting in an increase of action potential duration [4]. This last phenomenon seems to be related to a dysfunction of SK3 channels, which play a critical role in modulating the after-hyperpolarization [7].

Accordingly, recent immunohistochemical studies have localized SK3 to presynaptic nerve terminals, where they control the after-hyperpolarization [8]. As observed in neuromyotonia, an autoimmune disease caused by autoantibodies directed against VGKC, also oxaliplatin-*acute* neurotoxicity, is clinically characterized by motor nerve hyperexcitability, with a prolonged axonal after-activity following a single stimulus [9]. This means that a single nerve stimulation generates a CMAP closely followed by a high number of extra-discharges producing repeated oscillations arising in the distal portion of the peripheral nerve [1, 10, 11].

The EMG counterpart of this event consists in fibrillation potentials and repetitive bursts of spontaneous activity. Interestingly, SK3 channels are also expressed in adult denervated skeletal muscles where they contribute to hyperexcitability [12]. As mentioned by Dr Park, denervation-induced muscle hyperexcitability requires SK3 expression together with modifications in the function of other membrane ion channels [13]. It should be underscored,

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however, that nerve and muscle hyperexcitability are distinct neurophysiologic events, in which SK3 channels might play a different role. Thus, it remains plausible that oxaliplatin might have a direct effect on SK3 channels of the presynaptic nerve terminal, while causing, as direct or indirect effect, also a VGNaC dysfunction.

Moreover, Dr Park and colleagues have recently showed that, following oxaliplatin administration, sensory axons developed a significant decrease in refractoriness, suggesting a functional channelopathy of axonal Na⁺ channels, while motor axonal excitability remained unchanged [5]. The absence of motor nerve excitability is in contrast with several studies on *acute* oxaliplatin neurotoxicity, while the abnormalities in sensory nerves are frequent in *chronic* oxaliplatin-induced neurotoxicity. Thus, it cannot be excluded that changes in sensory nerve refractoriness demonstrated by Park and colleagues might be considered an early marker of *chronic* oxaliplatin neurotoxicity rather than the expression of *acute* neurotoxicity.

Taken together, these observations suggest that *acute* oxaliplatin-related neurotoxicity has a pathophysiological mechanism that is quite different from that of *chronic* neurotoxicity. For this reason, we totally agree with Dr Park that the evaluation of SK3 polymorphisms also in patients affected by chronic oxaliplatin-induced neurotoxicity might contribute to clarify this complex matter.

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