

Beta1 subunit-dependent modulation of BK channel by membrane cholesterol

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Background: The large conductance Ca^{2+} -activated K^+ (BK or Maxi-K) channels are ubiquitously expressed in different tissues without (brain, liver, etc) or with (smooth muscle and heart) regulatory beta-subunit, and play an important role in regulating various physiological processes such as cell excitability, hormone secretion, vascular activity, etc. Recent studies have shown that membrane cholesterol is a major regulator of several potassium channels including Kir and Kv1.5 channels. However, the regulation of BK channels by cholesterol is not fully understood.

Methods: Whole cell BK current and BK single channel current were recorded in whole-cell patch clamp mode and cell-attached single channel recording, respectively, in HEK 293 cells stably expressing Maxi-K gene or Maxi-K with beta1-subunit.

Results: We found that whole-cell BK current was significantly suppressed with cholesterol depletion by methyl-beta-cyclodextrin (MCD), whereas cholesterol-saturated-MCD had no effect on the current amplitude. Single channel recording showed that cholesterol depletion significantly reduced the open probability of BK channel, suggesting that cholesterol depletion likely decreases the membrane channel number. Interestingly, in cells stably expressing Slo and beta1-subunit, depletion of membrane cholesterol increased BK current, while cholesterol-saturated-MCD reduced BK current.

Conclusion: Our results demonstrate the important evidence that BK channels exhibit beta1-subunit-dependent responses to cholesterol. The enriched cholesterol reduces the activity of BK channels co-expressed with Max-K and beta1-subunit, which may at least in part accounts for the occurrence of hypertension in patients with high plasma cholesterol level, since beta-subunit transcripts are abundant in vascular smooth muscle.

Phase I/II trial of PTK787/ZK222584 combined with intravenous doxorubicin for treatment of patients with advanced hepatocellular carcinoma: implication for anti-angiogenic approach to hepatocellular carcinoma

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Background: This is a phase I/II trial aiming to assess the efficacy and tolerability of PTK787/ZK222584 (PTK) in combination with intravenous doxorubicin for the treatment of advanced hepatocellular carcinoma (HCC) patients.

Methods: In phase I, advanced HCC patients received PTK at escalating doses together with doxorubicin 60 mg/m² given as an intravenous bolus every 3 weeks to establish the maximum tolerated dose (MTD). Subsequently, in phase II, all patients received the same regimen with oral PTK at the MTD dose together with doxorubicin 60 mg/m² given as an intravenous bolus every 3 weeks for a maximum of 6 cycles.

Results: Nine patients were recruited in phase 1 part with the MTD established as 750 mg daily. Overall, 27 patients received the regimen with PTK at 750 mg daily. The median age was 52 (range, 23-73) years and 63% of patients were chronic hepatitis B carriers. Notably, the majority of patients had Child B cirrhosis. The overall response rate was 26.0% with all patients having partial response, and another 20% of patients achieved stable disease for at least 12 weeks. The median progression-free survival was 5.4 (0.27-23.6) months and overall survival was 7.3 (0.8-23.6) months. The commonest grade 3 or 4 non-haematological toxicities were mucositis (11%) and alopecia (7%), respectively. Grade 3 or 4 neutropenia was observed in seven (26%) patients with two having neutropenic sepsis.

Conclusion: The combination of PTK with intravenous doxorubicin shows synergistic activity in advanced HCC patients. Thus, the idea of combining anti-angiogenic agent together with chemotherapy may warrant further evaluation in future clinical trials of advanced HCC patients.