Sorafenib activates inflammasomes leading to sorafenib-induced immune related adverse events

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Background

Vascular endothelial growth factor (VEGF) promotes tumor angiogenesis through stimulating the proliferation and survival of endothelial cells. The severe adverse events caused by VEGF inhibitors might include immune-related ones; however, details of the mechanism have not been elucidated.

In this study, we tested whether axitinib, pazopanib, sorafenib, and sunitinib, which are tyrosine kinase inhibitors (TKIs) of VEGF receptor used for the therapy of renal cell carcinoma can activate inflammasomes in differentiated THP-1 cells, a human macrophage cell line. We also performed similar studies with semaxanib.

Methods

THP-1 cells were differentiated in medium for three days in a 24-well multiplate. On the fourth day, each well was incubated at 37 ℃ with 5% CO_2 for 24 h. Then the medium with or without drugs was added and incubated at 37 ℃ with 5% CO_2 for 24 h. The drug concentrations used in this study were within their therapeutic concentration (axitinib, 0.03–0.3 μM; pazopanib, 30–300 μM; semaxanib, 3–30 μM; sorafenib, 3–30 μM; sunitinib, 0.3–3 μM). YVAD (10 μg/mL) was used to inhibit caspase-1 activity. Protein samples from lysed cells (30 μg) or supernatants from THP-1 cells (20 μL) were performed Western blotting. IL-1β was measured in each culture medium sample using an ELISA kit. Caspase-1 activity was measured using the Caspase-Glo® 1 Inflammasome Assay. One-way analysis of variance (ANOVA) followed by Tukey's post-hoc test was used to assess for statistical significance ($P < 0.05$).

Results

Semaxanib and sorafenib induced the processing of caspase-1 and activated the inflammasome of differentiated THP-1 cells. Although pazopanib increased the production of IL-1β, canonical and non-canonical inflammasomes were not activated because caspase-1/4/5 was not activated in differentiated THP-1 cells. Axitinib and sunitinib did not activate inflammasomes of differentiated THP-1 cells within their therapeutic ranges.

Conclusions

Our results support the hypothesis that activation of inflammasomes contributes to the idiosyncratic reactions associated with semaxanib and sorafenib. Although pazopanib did not activate inflammasomes, it did cause increased IL-1β production, which may facilitate the induction of idiosyncratic reactions.

Key Words

Sorafenib, Vascular endothelial growth factor, Tyrosine kinase inhibitor, Inflammasome, Idiosyncratic drug reactions