FRAX597, a PAK1 inhibitor, synergises with gemcitabine in the reduction of pancreatic cancer growth

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Methods

The role of PAK1 was examined using stable PAK1 Knock-down clones generated by shRNA transfection of two human pancreatic cancer cell lines, PANC-1 and MiaPaCa-2. The effect of FRAX597, either alone or in combination with gemcitabine, on cell proliferation and migration in the human pancreatic cancer cell lines, PANC-1, MiaPaCa-2, and BxPC-3, and in the murine pancreatic cancer cell lines, Pan02 and LM-P, was examined in vitro by 3H-thymidine and Boyden chamber assays, respectively. The effect of FRAX597 and gemcitabine was assessed on tumour growth in vivo in an orthotopic pancreatic tail murine model.

Results

Knockdown of PAK1 resulted in inhibition of proliferation, an increase in gemcitabine sensitivity and a decrease in AKT and HIF1α expression. FRAX597 inhibited proliferation and migration in all pancreatic cancer cell lines in a dose-dependent manner. The combination of FRAX-597 and gemcitabine inhibited tumour growth in vitro and in vivo to a greater extent than either treatment alone.

Conclusion

PAK1 is an important player in mediating pancreatic carcinogenesis. PAK1 may play a role in gemcitabine metabolism and chemoresistance where the combination of a PAK1 inhibitor such as FRAX597 with gemcitabine could be a promising treatment for pancreatic cancer.

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