p38alpha is required for ovarian cancer cell metabolism and survival.


Source

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Abstract

INTRODUCTION:

Ovarian cancer is highly sensitive to chemotherapy but also shows a high rate of recurrence and drug resistance. These negative outcomes mostly depend on altered apoptotic pathways, making the design of new therapeutic strategies based on the induction of other types of cell death highly desirable. Several lines of research are now addressing cancer-specific features to specifically target tumor cells, thus reducing adverse effects. In this light, a great deal of attention has been devoted to the metabolic reprogramming occurring in cancer cells, which display increased levels of glycolysis compared with their normal counterparts. We recently showed that inhibition of p38alpha impairs key metabolic functions of colorectal cancer cells, inducing growth arrest, autophagy, and cell death both in vivo and in vitro. These effects are mediated by a switch from hypoxia-inducible factor 1alpha (HIF1alpha) to forkhead transcription factor O (FoxO)-dependent transcription.

METHODS:

We first characterized p38 expression in OVCAR-3, A2780, and SKOV-3 ovarian cancer cell lines. Then, we treated these cells with the p38alpha/p38beta-specific inhibitor SB202190 and performed a morphological, proliferation, and survival analyses. Finally, we studied HIF1alpha and FoxO3A expressions and signaling pathways to evaluate their role in SB202190-induced effects.

RESULTS:

p38alpha blockade induces the formation of intracellular autophagic vacuoles and reduces growth and viability of ovarian cancer cells. As in colorectal cancer, the underlying molecular mechanism seems to rely on a shift from HIF1alpha- to FoxO3A-dependent transcription, which is promoted by the activation of the adenosine monophosphate-activated protein kinase pathway.
CONCLUSIONS:

These data corroborate the hypothesis that pharmacological modulation of genes involved in cancer-specific homeostasis, such as p38alpha, might be exploited to design new therapeutic approaches to cancer treatment.

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