MOLECULAR & CELLULAR ONCOLOGY
2016, VOL. 3, NO. 2, e1062073 (2 pages)
http://dx.doi.org/10.1080/23723556.2015.1062073

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AUTHOR'S VIEW

OPEN ACCESS

Endosomal acidification inhibitors for the treatment of BRAF mutant tumors

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ABSTRACT

Mutations in *KRAS* and *BRAF* genes are commonly found in several types of cancer associated with poor prognosis and therapy resistance. We have identified phosphorylated p45-IKKα as an essential mediator of BRAF-induced tumorigenesis. Importantly, endosomal acidification inhibitors preclude phosphorylation of p45-IKKα and abolish the metastatic capacity of BRAF mutant cancer cells.

ARTICLE HISTORY
Received 8 June 2015
Revised 9 June 2015
Accepted 10 June 2015

KEYWORDS
Anti-cancer therapy; BRAK; colorectal cancer; endosomes; IKK

Colorectal Cancer (CRC) is the second leading cause of death by cancer in industrialized countries. Approximately 40% of these tumors carry mutation in the guanosine triphosphatase *KRAS* gene and an additional 15% are mutated in its downstream effector *BRAF* kinase, leading to stimulus-independent activation of the mitogen-activated protein/extracellular signal-regulated kinase (MAPK) pathway. Thus, it is not surprising that the occurrence of *KRAS* or *BRAF* mutations is predictive of non-response of patients to therapies based on antibodies against the epidermal growth factor receptor (EGFR).[1] Many

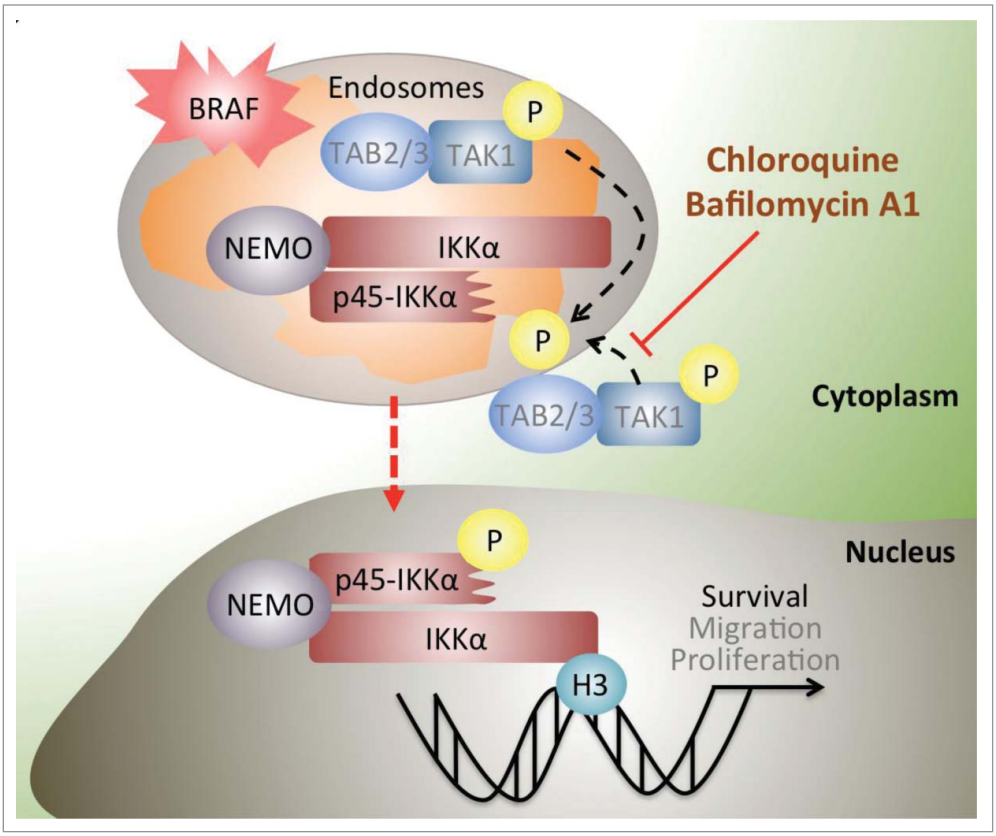

Figure 1. Mechanism of activation of p45-IKKα in the endosomal compartment. Phosphorylation of p45-IKKα takes place associated with the endosomes and requires activity of the TGFβ-associated kinase 1 (TAK1) complex. Activated p45-IKKα, together with full-length IKKα and the NF-κB essential modulator (NEMO), promotes specific gene transcription by direct binding to histone H3 (H3), which is precluded by endosomal acidification inhibitors such as chloroquine or bafilomycin A1.

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efforts are currently focused on circumventing this impediment through the development of novel BRAF and MEK inhibitors that could be used alone or in combination to treat not only patients with CRC, but also those with other malignancies such as melanoma, pancreatic cancer, or lung cancer. Although these inhibitors have already demonstrated an apparent therapeutic effect on different *BRAF* mutant tumors (such as melanoma, in which the prevalence of *BRAF* gene mutations is approximately 80%) their efficacy has been limited by the acquisition of multiple drug resistance.[2-5] In this scenario there is a clear need to identify novel therapeutic targets in the KRAS-BRAF pathway for the treatment of particular types of advanced/resistant cancer.

Recently, we identified a truncated form of the activated I kappa B kinase (IKK) α (p45-IKKα) that was specifically localized in the nucleus of CRC cells.[6] We have now demonstrated[7] that p45-IKKα is activated downstream of mutant KRAS and BRAF proteins and is absolutely required for CRC cell growth and invasion. Activation of p45-IKKα is independent of the nuclear factor kappa B (NF-κB) pathway and is associated with the endosomal compartment. Accordingly, inhibitors of endosomal acidification such as chloroquine or bafilomycin A1 completely blocked p45-IKKα phosphorylation (Fig. 1) without affecting activity of the NF-κB pathway, which is essential for most physiologic cellular functions. Using orthotopic xenografts as an *in vivo* model of CRC, we found that bafilomycin A1 and chloroquine enhanced the antitumoral effect of conventional chemotherapy (i.e., irinotecan or 5-azacytidine). Most notably, these agents totally suppressed the metastatic capacity of CRC cells with combined treatment. Our results highlight the therapeutic potential of drugs targeting specific NF-κB-independent IKK functions such as endosomal acidification inhibitors that exhibit a selective effect on BRAF mutated cells, thus explaining their reduced *in vivo* toxicity even in combined therapies. Our view is that chloroquine or chloroquine-derivatives could be rapidly translated into clinical practice in combination with standard chemotherapy for the treatment of BRAF mutated tumors including specific subtypes of CRC or metastatic melanoma. Moreover, inhibiting endosomal function could also limit the activity of other endosomal-dependent pathways such as Notch[8] and Wnt,[9] which constitute the driving force for several tumors by regulating cancer-initiating cell activity.

Finally, identifying the specific substrates of p45-IKKα activity in *BRAF* mutant cells (either phosphorylated proteins or genomic regions that directly interact with this kinase) should provide additional therapeutic targets for specific subsets of tumor, which will be explored in the near future.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

Acknowledgements

This work has been supported by Fundació La Marató de TV3 with grant # 20131210 and Instituto de Salud Carlos III-FEDER with grant # PI13/00448

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