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Selective Inhibitors of Genotoxic Stress-Induced IKK/NFκB Pathways for Cancer Therapy

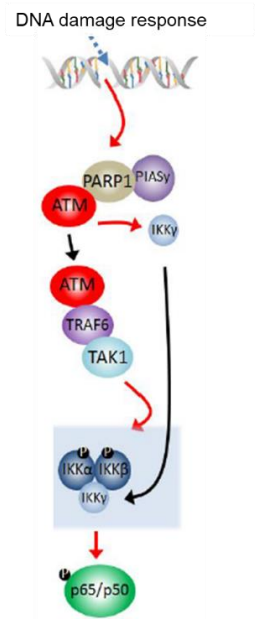
Keywords: Oncology, chemotherapy resistance, small molecule inhibitors, IKK/NF-κB, CLK

INVENTION NOVELTY

Many cancer therapies such as chemotherapeutics or irradiation induce cancer cell death through DNA damage and DNA double-strand break. In response to such genotoxic stress, cancer cells activate DNA damage response mechanisms leading to nuclear factor kappa B (NF-κB) activation via the IKK/NF-κB pathway which promotes cancer cell survival and is responsible for chemotherapy resistance. Thus, the IKK/NF-κB pathway represents an attractive drug target. However, IKK and NF-κB do have very diverse functions and general inhibition leads to blocking of beneficial effects and hence severe side effects. Researchers of the Max Delbrück Centrum developed a new class of pathway-tailored small molecule inhibitors (targeting CLK2 or CLK4) which interfere only with a stimulus-specific NF-κB activation, while leaving other modes of NF-κB activation intact.

VALUE PROPOSITION

The IKK/NF-κB pathway represents an attractive drug target since it is responsible for chemotherapy resistance which is a major hurdle for therapies involving genotoxic stress. General blocking of the IKK/NF-κB pathway is accompanied with severe side effects and not applicable for therapeutic intervention. The great innovation potential of the new compounds is the specific inhibition of the genotoxic stress-induced IKK/NF-κB sub pathway, while not interfering with other modes of NF-κB activation. In contrast to PARP inhibitors, which gained increasing attention as inhibitors of DNA damage repair, the named compounds block NF-κB activation in a cell type independent manner. The compounds offer a new promising therapeutic strategy to concomitantly reinforce chemotherapy and radiotherapy and may also have an interesting potential as stand-alone therapeutics in certain cancer types.



Inhibitors act upstream of IKK to block selectively DNA damage-induced signaling.

TECHNOLOGY DESCRIPTION

To identify selective inhibitors of genotoxic stress induced NF-kB signaling, a panel of different screening assays was developed which allowed to differentiate between NF-kB activation due to DNA double-strand break or due to activation by cytokines such as TNF-α or IL-1β. In the first round, a larger small molecule library was screened, and the resulting hits were further filtered according to drug-like properties.
The lead candidate selected for further profiling shows potent suppression of NF-kB signaling in several cell types in a cell type independent manner via targeting CLK2 and 4. Furthermore, the compound does not affect cytokine signaling and apoptotic cell death is significantly increased in tested cell lines. In parallel, a medicinal chemistry campaign was initiated, and the hit was expanded into lead series with lead-like properties. The lead series may be developed into potent compounds as add-on therapy for chemotherapy and irradiation therapy. In addition, the compounds may also have an interesting potential as stand-alone therapeutics in certain cancer types.

COMMERCIAL OPPORTUNITY

Available for licensing or collaboration.

DEVELOPMENT STATUS

In vitro proof of concept data in different cell lines is available.

PATENT SITUATION

Patents granted in Europe (EP3538529B1), USA (US11028084B2) and Australia (AU2017359276B2), pending in Japan (JP2019535709A5), China (CN109963850A) and Canada (CA3041832A1) with priority of 2017.
EP application for 2nd inhibitor-class filed in 2023.

FURTHER READING

Mucka P, Lindemann P, Bosco B, Willenbrock M, Radetzki S, Neuenschwander M, Brischetto C, Peter von Kries J, Nazaré M, Scheidereit C. CLK2 and CLK4 are regulators of DNA damage-induced NF-κB targeted by novel small molecule inhibitors. Cell Chem Biol. 2023 Jul 15:S2451-9456(23)00205-2. doi: 10.1016/j.chembiol.2023.06.027. Epub ahead of print. PMID: 37506701.

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