Minociclina diminui o mRNA do Rad51 inativando MKK1/2-ERK1/2 e diminui a viabilidade e a proliferação da linhagem A549 e H1975

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Minocycline enhances mitomycin C-induced cytotoxicity through down-regulating ERK1/2-mediated Rad51 expression in human non-small cell lung cancer cells.

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Abstract

Minocycline is a semisynthetic tetracycline derivative; it has anti-inflammatory and anti-cancer effects distinct from its antimicrobial function. However, the molecular mechanism of minocycline-induced cytotoxicity in non-small cell lung cancer (NSCLC) cells has not been identified. Rad51 plays a central role in homologous recombination and high levels of Rad51 expression are observed in chemo- or radioresistant carcinomas. Our previous studies have shown that the MKK1/2-ERK1/2 signal pathway maintains the expression of Rad51 in NSCLC cells. In this study, minocycline treatment inhibited cell viability and proliferation of two NSCLC cells, A549 and H1975. Treatment with minocycline decreased Rad51 mRNA and protein levels through MKK1/2-ERK1/2 inactivation. Furthermore, expression of constitutively active MKK1 (MKK1-CA) vectors significantly rescued the decreased Rad51 protein and mRNA levels in minocycline-treated NSCLC cells. However, combined treatment with MKK1/2 inhibitor U0126 and minocycline further decreased the Rad51 expression and cell viability of NSCLC cells. Knocking down Rad51 expression by transfection with small interfering RNA of Rad51 enhanced the cytotoxicity and cell growth inhibition of minocycline. Mitomycin C (MMC) is typically used as a first or second line regimen to treat NSCLC. Compared to a single agent alone, MMC combined with minocycline resulted in cytotoxicity and cell growth inhibition synergistically in NSCLC cells, accompanied with reduced activation of phospho-ERK1/2, and reduced Rad51 protein levels. Overexpression of MKK1-CA or Flag-tagged Rad51 could reverse the minocycline and MMC-induced synergistic cytotoxicity. These findings may have implications for the rational design of future drug regimens incorporating minocycline and MMC for the treatment of NSCLC.

KEYWORDS:

ALLN (PubChem CID: 4332); Actinomycin D (PubChem CID: 2019); Crystal violet (PubChem CID: 11057); Cycloheximide (PubChem CID: 6197); ERK1/2; MG132 (PubChem CID: 462382); Minocycline; Minocycline (PubChem CID: 54675783); Mitomycin C; Mitomycin C (PubChem CID: 5746); Non-small cell lung cancer; Penicillin (PubChem CID: 5904); Sodium bicarbonate (PubChem CID: 516,892); Streptomycin (PubChem CID: 19649); Trypan blue (PubChem CID: 9562061); U0126 (PubChem CID: 3006531); l-glutamine (PubChem CID: 5961)

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