

# 4-IPP, a selective MIF inhibitor, causes mitotic catastrophe in thyroid carcinomas

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## Abstract

Macrophage migration inhibitory factor (MIF) is a pro-inflammatory cytokine that is over-expressed in several human neoplastic cells. When MIF binds its receptor (CD74) and co-receptor (CD44), it initiates signaling cascades that orchestrate cell proliferation and survival, and it can directly modulate the activity of AMPK. These activities indicate that MIF potentially regulates cell survival and metabolism. We found that MIF was primarily co-expressed with CD74 in 16 out of 23 papillary thyroid carcinoma (PTC) and in all the 27 available anaplastic thyroid carcinoma (ATC) biopsy samples. MIF and CD74 were co-expressed in TPC-1 and HTC-C3 cell lines. The selective MIF inhibitor, 4-iodo-6-phenylpyrimidine (4-IPP), blocked MIF/CD74 internalization, activated JNK, and dose-dependently inhibited proliferation inducing apoptosis and mitotic cell death. In two CD74-negative cell lines, NIM-1 and K1, 4-IPP treatment partially reduced proliferation. Coordinated MIF and CD74 expression appeared to confer in tumor cells the plasticity necessary to escape cell cycle regulation, metabolic changes, and stress conditions. MIF/CD74 signaling removal made cells susceptible to apoptosis and mitotic cell death. This finding suggests a possible avenue for targeting DNA endoreduplication, thus preventing the proliferation of therapy-resistant cell subpopulations. This study highlights MIF/CD74 axis as an important player in the biology of aggressive thyroid neoplasms.

## Key Words

- ▶ papillary thyroid carcinoma
- ▶ anaplastic thyroid carcinoma
- ▶ macrophage migration inhibitory factor
- ▶ CD74
- ▶ 4-IPP
- ▶ AMPK
- ▶ endoreduplication

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