Wnt/IL-1β/IL-8 autocrine circuitries control chemoresistance in mesothelioma initiating cells by inducing ABCB5.

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Abstract

Malignant pleural mesothelioma (MPM) is a tumor with high chemoresistance and poor prognosis. MPM-initiating cells (ICs) are known to be drug resistant, but it is unknown if and how stemness-related pathways determine chemoresistance. Moreover, there are no predictive markers of IC-associated chemoresistance. Aim of this work is to clarify if and by which mechanisms the chemoresistant phenotype of MPM IC was due to specific stemness-related pathways. We generated MPM IC from primary MPM samples and compared the gene expression and chemo-sensitivity profile of IC and differentiated/adherent cells (AC) of the same patient. Compared to AC, IC had upregulated the drug efflux transporter ABCB5 that determined resistance to cisplatin and pemetrexed. ABCB5-knocked-out (KO) IC clones were resensitized to the drugs in vitro and in patient-derived xenografts. ABCB5 was transcriptionally activated by the Wnt/GSK3β/β-catenin/c-myc axis that also increased IL-8 and IL-1β production. IL-8 and IL-1β-KO IC clones reduced the c-myc-driven transcription of ABCB5 and reacquired chemosensitivity. ABCB5-KO clones had lower IL-8 and IL-1β secretion, and c-myc transcriptional activity, suggesting that either Wnt/GSK3β/β-catenin and IL-8/IL-1β signaling drive c-myc-mediated transcription of ABCB5. ABCB5 correlated with lower time-to-progression and overall survival in MPM patients treated with cisplatin and pemetrexed. Our work identified multiple autocrine loops linking stemness pathways and resistance to cisplatin and pemetrexed in MPM IC. ABCB5 may represent a new target to chemosensitize MPM IC and a potential biomarker to predict the response to the first-line chemotherapy in MPM patients.

KEYWORDS:
ABCB5; chemoresistance; initiating cells; malignant pleural mesothelioma