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JWA based dysregulations of signal pathway in cisplatin resistance of human gastric cancer

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Drug resistance is a big challenge in platinum based cancer chemotherapy in solid tumors including gastric cancer (GC). Enhancement of DNA repair capability in platinum treated cancer cells is one of major characteristics although several other mechanisms are involved in development of plutinum resistance. JWA is a multifunctional molecule and participates several important signal pathway regulations including base excision repair (BER) in both normal epitherial and cancer cells. We established cisplatin resistant BGC823/DDP and SGC7901/DDP GC cells by gredient increase of cisplatin exposure concentrations in cell culture medium; we systimatically investigated the features of signal pathways and related mechanisms in both primary/secondary cisplatin resistant GC cells and in xenograft mice models. We discovered that JWA based dysregulation of cellular signal pathways played important roles in cisplatin resistacne. Our data was showing that downregulated JWA expression-driven overactivations of XRCC1 linked BER and DR4 linked signal pathways contributed to cisplatin resistance in GC cells. Furthermore, we identified E3 ligase RNF185 is responsible for JWA degradation. In addition, as a mimic of JWA protein, JWA peptide targetted to MMP2, inhibited proliferation and metastasis in both cisplatin sensitive and resistant GC cells. Therefore JWA peptide has a potential for development of new drug to anti-cisplatin resistance.

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