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Platinum pathway

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Description

Platinum (Pt)-containing drugs are currently used in the clinic for treating various types of cancers, including testicular germ-cell tumors, small cell lung cancer, colon carcinoma, ovarian cancer, head and neck cancer, bladder cancer, lymphomas, and sarcomas [1,2]. Pt is the 78th element in the periodic table and has been used in medicine since the mid 1960's. The major Pt-containing drugs are cisplatin, carboplatin, and oxaliplatin. They destroy cancerous cells by interfering with the DNA, through interstrand and intrastrand crosslinks, and DNAprotein crosslinks, thereby preventing cell division and growth [3,4].

Although Pt-based drugs are the most widely used in cancer treatment, many tumors are completely resistant to these drugs and no clinical response is attained. The difference in clinical response is thought to be due, in part, to the pharmacokinetics of these drugs. The influx of Pt drugs into the cell is regulated by SLC31A1 (CTR1) and the efflux by ABCC2, ABCG2, ATP7A, and ATP7B [5–10] (Fig. 1). ATP7A is involved in the copper transport from cytoplasm into trans-Golgi network, where it serves to export copper from the cell through the vesicular secretory pathway. ATP7B is also an exporter of copper and is localized to the trans-Golgi network. When the copper content of the cell increases, ATP7A moves from trans-Golgi network to the plasma membrane and ATP7B relocates to

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intracellular vesicular compartments, presumably involved in the export pathway. Once Pt is inside the cell, the primary antitumor mechanism is the formation of Pt-DNA adducts which lead to cell-cycle arrest and apoptosis [3]. HMGB1 is important in the cell recognition of these Pt-DNA adducts, and therefore signals cellular response to these adducts [11,12]. Genes involved in mismatch repair, such as MSH6 and MLH1 [12], decrease the cell-sensitivity to these drugs. In addition, nucleotide excision repair is mediated by XRCC1, ERCC1, ERCC2, and XPA, and known variants in these genes affect patient's response to Pt-based drugs [13–19]. These genes act by detecting single-strand breaks and removing proteins from the DNA helix, which then becomes more accessible to repair enzymes. POLH and POLB variants have been shown to provide tolerance to Pt-based drugs, and therefore represent an important determinant of the cellular response to Pt drugs [12–21]. In addition, there are several genes, such as MPO, SOD1, GSTM1, NQO1, GSTP1, and MT that are responsible for lowering the intracellular concentration of Pt drugs and therefore play a key role in cellular resistance to these drugs [22–26]. Patients who carry certain alleles of these detoxification-related genes have been shown to have differences in survival due to variation in drug sensitivity and adverse drug reactions [27–29].

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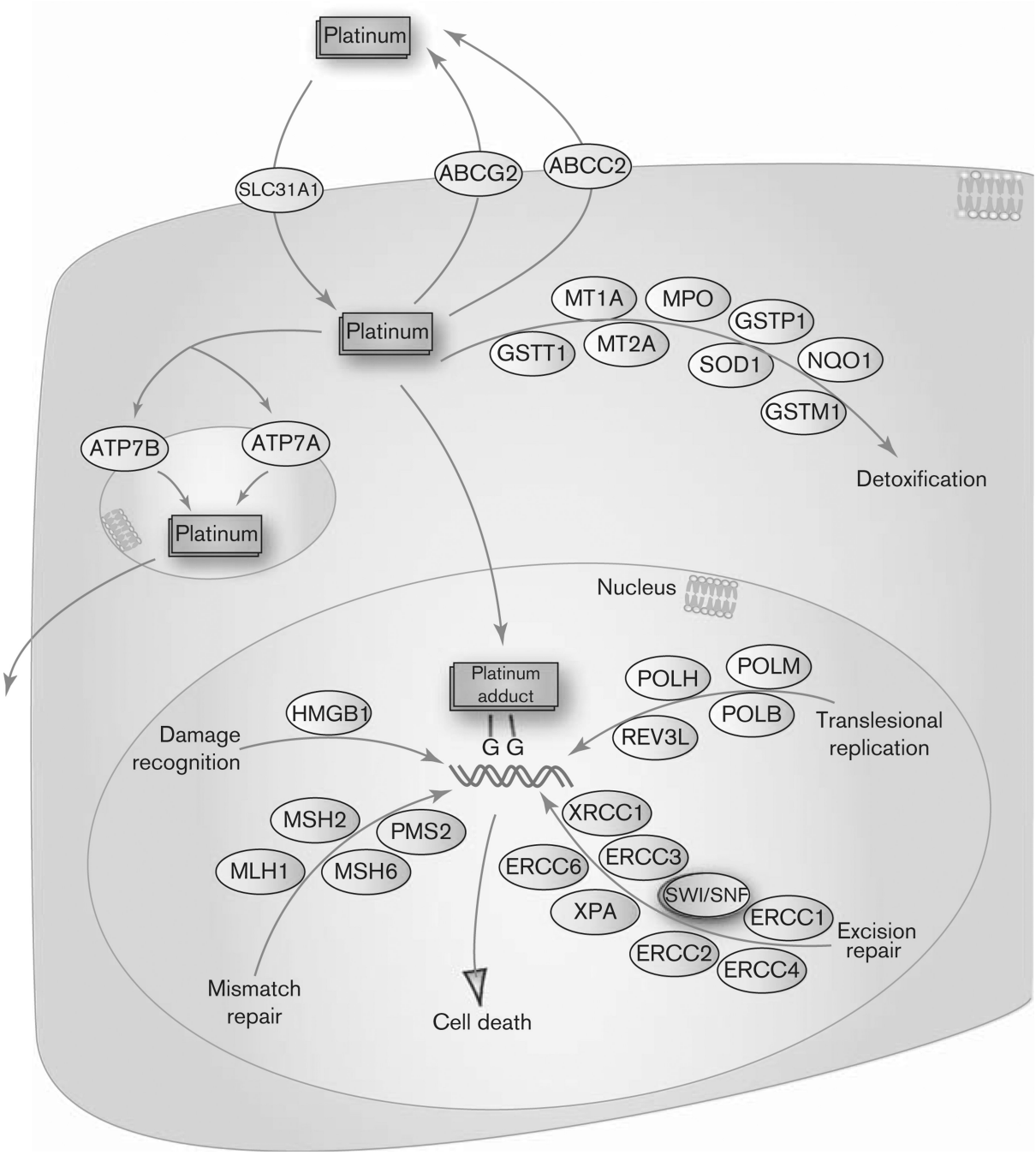

Fig. 1.

Representation of the candidate genes involved in the metabolism, transport, and cellular effect of platinum containing drugs.