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Chemotherapy Prediction Using DNA Methylation Biomarkers

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Introduction

Platinum-based agents (cisplatin (CDDP), carboplatin, and oxaliplatin) are widely used to treat various cancers. Despite their broad clinical application, several concerns remain, particularly the emergence of treatment resistance, which adds to the challenges. Epigenetic biomarkers, particularly those related to DNA methylation, have increasingly demonstrated their value as cancer biomarkers, allowing for simple, fast, and low-cost detection in a non- or minimally invasive manner. These are extremely versatile, with applications in diagnosis, risk stratification, and prediction of response to a specific treatment, saving patients from potentially harmful and unnecessary side effects.

However, the development and validation of a reliable biomarker with a strong routine clinical application is a lengthy process that includes many steps ranging from in vitro experiments to in vivo pre-clinical model validation and patient tissue analysis, followed by further validation in independent (multi-institutional) cohorts to ensure the desired high sensitivity, specificity, and accuracy. Indeed, there are numerous studies proposing new biomarkers, but very few have made it to clinical practice for a variety of reasons, including pre-analytical issues, cohort demographic differences, and a lack of standardized reporting, among others. We focused on epigenetic-based biomarkers, specifically DNA methylation [1,2], that could be used to predict response to platinum-based chemotherapy in this review, emphasizing their development and detection methods.

Description

Platinum-based chemotherapy is widely used in cancer treatment, making research into its mechanism of action and resistance critical for modern oncology. Although CDDP is still the most commonly used platinum drug in the clinic, two analogues for tumors types have been approved: carboplatin and oxaliplatin [3]. For many years, CDDP has been used as a first-line treatment for a variety of cancers, either alone or in combination with other therapies such as radiation (to act as a radio sensitizer) or other chemotherapeutics. It is typically used as a neoadjuvant (to shrink the tumour) or adjuvant (to reduce the risk of recurrence) therapy. Because of its cytotoxic activity, it may also be used in palliative chemotherapy [4,5] to maintain patient quality of life.

The disadvantage is that platinum agents have several serious side effects, such as nephrotoxicity and peripheral neurotoxicity, which limits the dose that can be used for patient treatment. Furthermore, cancer survivors who were previously treated with platinum have traceable levels of CDDP in urine and plasma many years after treatment, which is a major concern that may cause long-term side effects, resulting in a decline in quality of life and, eventually, death. The current precision medicine paradigm is no longer capable of sustaining such side effects in the short or long term, and all efforts must be directed toward improving risk stratification of patients using appropriate biomarkers in order to save patients from futile, unnecessary treatments and their side effects. One platinum atom is bound to two chloride atoms and two amide groups to form CDDP, or cis-diamminedichloroplatinum (II).

CDDP can cross the cell membrane via passive diffusion or transmembrane transporters, the most studied of which are the copper transporters CTR1 and CTR2. Because of the chloride concentration, the cytosol promotes the equation process of CDDP.Once inside the cell, CDDP binds strongly to the N7 reactive Centre of purine residues, causing DNA damage through adduct formation, preventing cell division, and resulting in apoptotic cell death. Although CDDP, carboplatin, and oxaliplatin may cause different DNA adducts, the fundamental cellular processes associated with the CDDP mechanism are not fully understood and are being researched.

Conclusion

The fundamental distinction between genetic and epigenetic changes is that genetic lesions are irreversible, whereas epigenetic lesions are potentially reversible because they are associated with changes in DNA methylation or other chromatin modifications, allowing for therapeutic intervention. Epigenetic mutations, also known as epimutations, are heritable; they can be constitutional and derived from a germline, and thus expected to be found in all of an individual's tissues, or they can be somatic and eventually restricted to a specific somatic tissue. Abnormal patterns of DNA methylation, disrupted patterns of histone posttranslational modifications (PTMs), altered expression of small non-coding RNAs, and changes in chromatin composition and/or organisation are examples of epigenetic aberrations.

DNA methylation primarily affects CpG dinucleotide and is involved in tumor genesis via three main mechanisms: locus-specific (e.g., tumor suppressor genes (TSG)) hyper methylation, cancer genome global hypo methylation, or direct mutagenesis of sequences. It is worth noting that all three routes occur concurrently, emphasizing the significance of methylation as an epigenetic driver in cancer development. Hyper methylation has a negative impact on transcription by lowering the levels of proteins involved in processes such as DNA damage repair, resulting in a fundamental replication advantage over normal cells.

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