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Review

Role of nucleotide excision repair proteins in response to DNA damage induced by topoisomerase II inhibitors

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ABSTRACT

In cancer treatment, chemotherapy is one of the main strategies used. The knowledge of the cellular and molecular characteristics of tumors allows the use of more specific drugs, making the removal of tumors more efficient. Among the drugs of choice in these treatments, topoisomerase inhibitors are widely used against different types of tumors. Topoisomerases are enzymes responsible for maintaining the structure of DNA, altering its topological state temporarily during the processes of replication and transcription, in order to avoid supercoiling and entanglements at the double helix. The DNA damage formed as a result of topoisomerase inhibition can be repaired by DNA repair mechanisms. Thus, DNA repair pathways can modulate the effectiveness of chemotherapy. Homologous recombination (HR) and non-homologous end joining (NHEJ) are the main pathways involved in the removal of double strand breaks (DSBs); while nucleotide excision repair (NER) is mainly characterized by the removal of lesions that lead to significant structural distortions in the DNA double helix. Evidence has shown that DSBs are the main type of damage resulting from the inhibition of the DNA topoisomerase II enzyme, and therefore the involvement of HR and NHEJ pathways in the repair process is well established. However, some topoisomerase II inhibitors induce other types of lesions, like DNA adducts, interstrand crosslinks and reactive oxygen species, and studies have shown that other DNA repair pathways might be participating in removing injury induced by these drugs. This review aims to correlate the involvement of proteins from different DNA repair pathways in response to these drugs, with an emphasis on NER.

Contents

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1. DNA topoisomerases

Topoisomerases are well described enzymes that control DNA supercoiling and entanglements introducing temporary single or double strand breaks in DNA, thus being essential in maintaining the integrity of DNA during transcription and replication processes. In mammalian cells, there are three types of topoisomerases: type I, type II and type III [1–3]. The two major classes, type I and type II, are distinguished by the number of DNA strands that they cleave and the mechanism by which they alter the topological properties of the genetic material [3,4]. Despite their differences in specificity, their catalytic mechanism is a common feature between the different types of enzyme. In all cases, this mechanism consists of a nucleophilic attack of a DNA phosphodiester bond by a catalytic tyrosine residue from the topoisomerase, but while type I enzymes cleave only one strand of DNA for catalysis, those in type II cleave both strands to overcome the entanglements or to avoid supercoiling (Fig. 1). The intermediates formed in this process are commonly referred to as cleavable complexes [1,3,4].

Eukaryotic type I topoisomerases (topo I) are monomeric enzymes organized in two classes: topo IA cleaves a single-strand segment and then allows the intact single strand to pass through the break, needs divalent metal ions for DNA scission and attaches covalently to the 5′-terminal phosphate of the DNA; whereas topo IB works by letting the broken strand rotate around the intact strand, does not require divalent metal ions and covalently links to the 3′-terminal phosphate [1,4]. These enzymes require no high energy co-factor and despite modulating DNA under- and over-winding, they are not able to remove knots or tangles from duplex DNA [4].

Eukaryotic type II topoisomerases (topo II) cleave both DNA-strands and let the duplex pass through the breakage [1–3]. These enzymes function as homodimers and require divalent metal ions and adenosine triphosphate (ATP) for complete catalytic activity [3,4]. Mammals have two isoforms of topo II, topoisomerase IIα and topoisomerase IIβ, which are closely related, but are encoded by separate genes and also differ in their molecular masses; topo IIα has 170 kDa, while topo IIβ has 180 kDa [3–6]. The two enzymes show distinct patterns of expression and physiological functions in vertebrate cells. Topo IIα is essential for the survival of proliferating cells and its levels are regulated over the cell cycle, showing concentration peaking in G2/M. This isoform is associated with replication forks and remains tightly bound to chromosomes during mitosis. Topo IIβ, on the other hand, shows an independent status in relation to the proliferation and dissociates from chromosomes during mitosis. This isoform cannot compensate for the loss of topo IIα in mammalian cells, suggesting that both enzymes have their own and different roles [4,7,8].

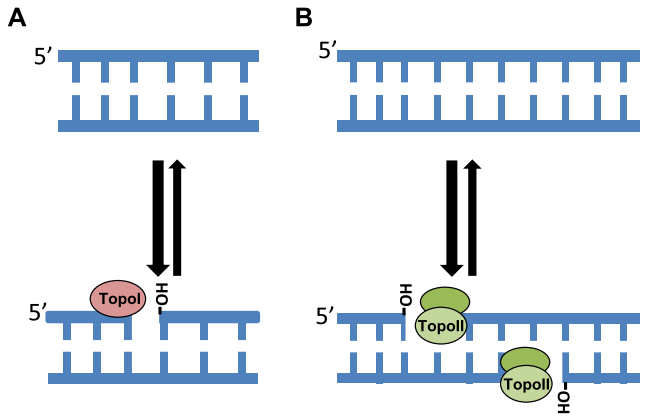

Fig. 1. Different action mechanisms of topoisomerase I and II in the formation of DNA cleavage complexes. (A) Topoisomerase IB cleaves a single DNA strand forming a covalent complex at the 3′-end of the breaks. (B) The action of topoisomerase II in both DNA-strands, forming the covalent complexes at 5′-end of the breaks.

2. Topoisomerase inhibitors

Topoisomerase inhibitors are among the most effective and most commonly used anticancer drugs. The main target of these inhibitors is the DNA cleavage/ligation step in the catalytic cycle of the enzyme, preventing the ligation of breaks generated by topoisomerases. Consequently, there is an increase of the cleavable complexes, which are converted in DNA damage during replication and transcription. Moreover, there are important selectivity and non-ambiguity characteristics in these drugs in view of the fact that clinically relevant topo I inhibitors do not affect topo II, and nor do topo II inhibitors affect topo I [1,2].

2.1. Topoisomerase I inhibitors

Camptothecin (CPT), an alkaloid isolated from the plant *Camptotheca acuminata* in the 1960s, was the first topo I inhibitor identified having antitumor properties, although its mechanism of action was only discovered about 20 years later [9]. There are now semi-synthetic derivatives of CPT approved by the FDA (Food and Drug Administration). Fig. 2A shows the structures of some topo I inhibitors and the presence of an α-hydroxylactone E-ring. One of the CPT derivatives, topotecan, is already used in clinical routines, being prescribed for ovarian cancer and recurrent small cell lung cancer. Another FDA-approved CPT derivative is irinotecan, a prodrug that needs to be converted into its active metabolite SN-40, and is recommended mainly for gastrointestinal tumors. There are some common side effects of this drug, such as diarrhea, which can be severe, temporary liver dysfunction, and myelosuppression, which also occurs in topotecan treatment [1,9].

An important limitation in all CPT derivatives is that they are rapidly (within minutes) and spontaneously inactivated as a consequence of the E-ring opening, changing from the lactone form to the carboxylate form, which is favored by the physiological neutral pH. Moreover, this form tightly binds to serum albumin, depleting in consequence the lactone form that contains the intact E-ring [1,2]. In addition to this characteristic, these drugs also have other limitations, such as the rapid reverse of the cleavable DNA-topo I complex after drug removal, which imposes the necessity of long infusions for patients, the overexpression induction of the drug efflux membrane transporters (glycoprotein-P), which generates a cross-resistance to CPT derivatives, and the side-effects which are dose-limiting [1,10]. To overcome all these limitations, non-camptothecin derivatives are currently in clinical development and in clinical trials. The indenoisoquinolines were the first non-camptothecin topo I inhibitors discovered that offer several advantages over the camptothecins. They are chemically more stable, present more persistent cleavage complexes and can overcome multidrug resistance by drug efflux pumps [10]. These compounds are derived from a 3-arylisoquinoline structure, a precursor in the development of various topo I inhibitors with a 3-arylisoquinoline nucleus [11].

2.2. Topoisomerase II inhibitors

Unlike topo I inhibitors, there are more classes of drugs that target topo II enzymes. In addition to drugs that increase the levels of cleavable complexes, some topo II inhibitor drugs are presumed to act primarily by inhibiting the catalytic site, preventing the ligation of the enzyme to the DNA. These differences give rise to the different names for topoisomerase inhibitors; in the first case we