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Review

Regulatory players of DNA damage repair mechanisms: Role in Cancer Chemoresistance

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ABSTRACT

DNA damaging agents are most common in chemotherapeutic molecules that act against cancer. However, cancer cells possess inherent biological features to overcome DNA damages by activating various distinct repair mechanisms and pathways. Importantly, various oncogenes, cancer stem cells (CSCs), hypoxic environment, transcription factors and bystander signaling that are activated in the cancer cells influence DNA repair, thereby effectively repairing the DNA damage. Repaired cancer cells often become more resistance to further therapy and results in disease recurrence. In this review, we summarize how the various signaling pathways in cancer cells regulates DNA repair and induce chemoresistance.

Contents

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1. Introduction

Cancer cells acquire resistance to chemotherapeutic agents by altering the cell survival mechanisms (cell cycle arrest and repair), apoptosis pathway, cancer stem cells, chemical and biological properties of the drug, detoxification of therapeutic agents (drug-target interactions) and DNA damage and repair pathways (Fig. 1). DNA damage response (DDR) is an important pathway that cells undertake to repair the multiple DNA damages that occur both endogenously and exogenously. Especially post-translational modifications like phosphorylation, ubiquitination, sumolyation that happens on the DNA damage response proteins are essential for proper repair [1]. Deficiency of DNA repair proteins will mostly result in the cell death, alternatively the cells may undergo genomic instability based on the magnitude of the damage. Moreover, mutation in the DNA repair genes such as FANCD2 (Fanconi Anemia Complementation Group D2), BRCA1, BRCA2 (Breast Cancer Gene) and ATM (Ataxia-Telangiectasia Mutated gene; also called as ATM serine/threonine kinase) results in the compromised DNA repair in normal cells which often leads to syndromes associated with genomic instability. More mutations in DNA repair genes and their relevance to tumors are reviewed elsewhere [2]. Accumulation of these DNA damages in the unrepaired cells results in genomic instability that ultimately leads to carcinogenesis [3]. Taking advantage of the significance of DNA damage and repair mechanism for cell survival, biological and research scientists have started to induce DNA damage in cancer cells as a therapeutic approach. The uncontrollable growth of cancer cells are inhibited by the use of radiotherapy or chemotherapy. It is important to note that radiation and most of chemotherapeutics act by inducing DNA damage in actively replicating cancer cells [4]. For example, platinum drugs (platins) which include cisplatin, carboplatin and oxaliplatin used for ovarian cancer treatment induce inter and intra-strand crosslinks [5]. Drugs like CPT (camptothecin: topoisomerase inhibitors) inhibit re-ligation of DNA strands leading to double strand breaks (DSB) [6]. Olaparib inhibits the single strand break (SSB) repair protein PARP (Poly ADP-Ribose Polymerase) after which the SSB gets converted into DSB in actively replicating cancer cells [7]. While DNA damage response pathway is important for normal cell survival, the same pathway is also adapted extensively to overcome the damage induced by therapeutic agents in cancer cells, thus inducing chemoresistance. Specifically, DNA repair mechanisms are regulated by various oncogenic signaling molecules in the cancer cells. Repair of these chemotherapeutic agents induced DNA damage results in chemoresistance. This chemo resistive phenotype cancer cells are one among the common causes for disease recurrence and the most aggressive type of tumors. In the present review, we will summarize how different signaling mechanisms in cancer cells regulate the DNA repair proteins causing chemoresistance. Particularly, we discuss here, how various signaling molecules that are involved in the

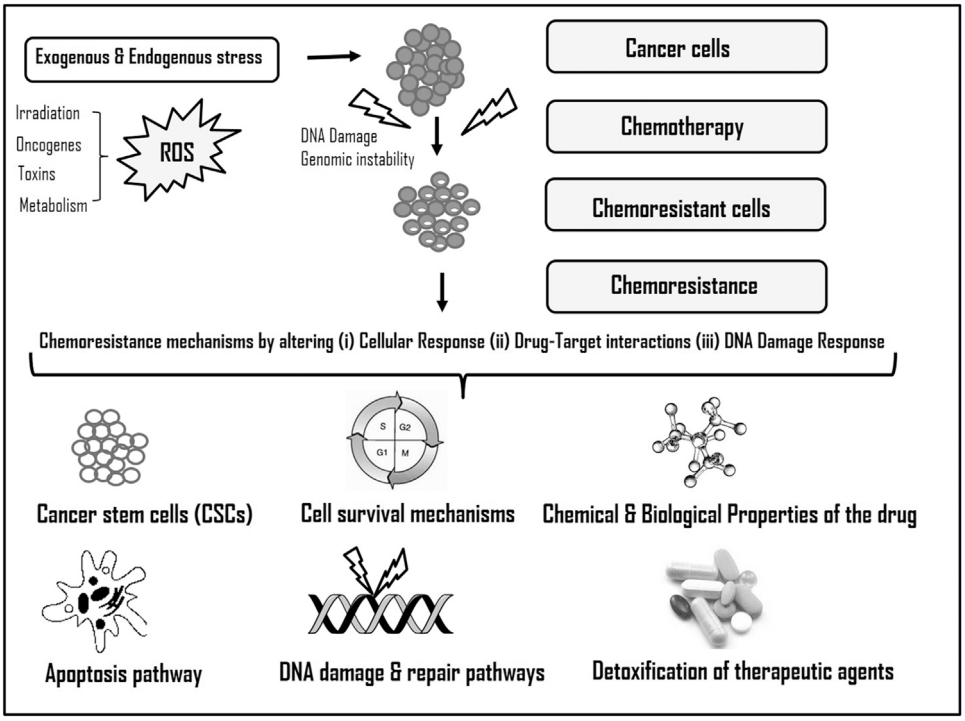

Fig. 1. The main chemoresistance mechanisms of cancer cells by altering the (i) cellular response include cell survival mechanisms, cancer stem cells and apoptosis pathway, (ii) drug-target interactions include chemical & biological properties of the drug and detoxification of therapeutic agents (iii) DNA damage and repair pathways.