Drug-induced formation of DNA inter-strand crosslinks

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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

14/11/2022
**Introduction**

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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**Literature references**


Reactome database release: 82

This document contains 1 pathway and 2 reactions (see Table of Contents)

https://reactome.org
Drug-induced formation of DNA interstrand crosslinks

Stable identifier: R-HSA-9750126

This pathway describes how drugs commonly used in the treatment of cancer, psoriasis and severe atopic dermatitis produce DNA interstrand crosslinks that are repaired through the Fanconi anemia pathway. For review, please refer to Deans and West 2011, Fu et al. 2012, and Rycenga and Long 2018.

Literature references


Editions

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Some of the earliest and still most widely used anti-cancer chemotherapeutics are drugs that induce DNA interstrand crosslinks (ICLs). In addition to inducing ICLs, these drugs also induce other types of DNA damage. ICL-inducing anti-cancer agents can be grouped into monofunctional alkylating agents (chloroethylating nitrosoureas), bifunctional alkylating agents (nitrogen mustards, aziridines and pyrrolobenzodiazepine dimers), platinums, and psoralens (furocoumarins). All ICL-inducing drugs are characterized by the presence of two chemical leaving groups that are lost in the formation of the ICL.

Chloroethylating nitrosoureas are monofunctional alkylating agents that induce DNA crosslinks in two steps: chloroethylation of a nucleophilic site on one strand, followed by displacement of chlorine by a nucleophilic site on the opposite strand, resulting in an ethyl bridge between the strands. Chloroethylating nitrosoureas include the following chemotherapeutic drugs:

carmustine (also known as BCNU) (Kohn 1977: study done on E. coli DNA)
fotemustine (Hayes et al. 1997)
lomustine (also known as CCNU) (Kohn 1977: study done on E. coli DNA)
nimustine (also known as ACNU) (Aida and Bodell 1987).

Nitrogen mustards are alkylating agents that include the following chemotherapeutic drugs:

chlorambucil (Hartley et al. 1999; Wang et al. 2003)
cyclophosphamide (Crook et al. 1986)
ifosfamide (Hartley et al. 1999)
mechlorethamine (Sunters et al. 1998)
melphalan (Parsons 1984)
uramustine (O'Connor and Kohn 1990: study done in mouse cells).
Aziridines are bifunctional alkylating agents that include the following chemotherapeutic drugs: altretamine (Coley et al. 1995: trimelamol, the compound assayed in the study, contains three carbino-lamine moieties, thus representing a bioactivated form of altretamine, also known as HMM) mitomycin C (also known as MMC), an antitumor antibiotic potent at inducing ICLs (Dorr et al. 1985) thioTEPA (Cohen et al. 1991: study done in mice).

Pyrrrolobenzodiazepine (PBD) dimers are derivatives of naturally occurring anti-tumor antibiotics. While naturally occurring anti-tumor antibiotics anthramycin, DC-81, tomamycin and sibiromycin do not induce ICLs, joining two PBD molecules through their C8 positions via a linker creates potent bifunctional agents able to induce ICLs (Smellie et al. 1994). PBD dimers that have been clinically tested are: SGD-1882, used to produce talirine (also known as SGD-1910), which can be conjugated with antibodies (Kung Sutherland et al. 2013: direct induction of ICLs by SGD-1882 has not been shown, but addition of SGD-1882 induces appearance of DNA damage response biomarkers consistent with ICL repair) SG3199 (Hartley et al. 2018), used to produce tesirine (also known as SG3249), which contains a linker added onto SG3199, which enables its conjugation with antibodies (Tiberghien et al. 2016) SG2000 (also known as SJG-136, Gregson et al. 2001)

Due to their potency, PBD dimers are finding their use in the clinic as antibody-drug conjugates, which allows targeted delivery of these drugs to cancer cells (reviewed in Hartley 2021).

Platinums are platinum (Pt)-containing compounds that include the following chemotherapeutic drugs: carboplatin (Blommaert et al. 1995) cisplatin (Plooy et al. 1985, Blommaert et al. 1995) oxaliplatin (Woynarowski et al. 1998) picoplatin (also known as AMD473) (Holford, Sharp et al. 1998; Holford, Raynaud et al. 1998) satraplatin.(Mellish et al. 1995).


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Psoralens in combination with UV generate DNA interstrand crosslinks

**Location:** Drug-induced formation of DNA interstrand crosslinks

**Stable identifier:** R-HSA-9713837

**Type:** omitted

**Compartments:** nucleoplasm

Psoralens (fucocoumarins) are plant-derived chemicals that, in the presence of UV light, create DNA interstrand crosslinks (ICLs) along with other types of DNA lesions. PUVA is a combination therapy consisting of psoralens and UV light, used to treat skin conditions such as psoriasis and severe atopic dermatitis (eczema), as well as the cutaneous T-cell lymphoma (mycosis fungoides). The following psoralens have been widely used in the PUVA therapy:

- 8-methoxypsoralen (Cohen et al. 1981; Gruenert et al. 1985)
- 5-methoxypsoralen (Gruenert et al. 1985)
- trimethylpsoralen (also known as trioxalen) (Carter et al. 1979).

The PUVA therapy increases the risk of different types of skin cancer, such as basal carcinoma, squamous cell carcinoma, and melanoma. For review, please refer to Deans and West 2011.

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</tr>
</tbody>
</table>

https://reactome.org
Table of Contents

Introduction

Drug-induced formation of DNA interstrand crosslinks

Anti-cancer drugs generate DNA interstrand crosslinks

Psoralens in combination with UV generate DNA interstrand crosslinks

Table of Contents