Mutational signatures in cancer caused by alkylating agents

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INTRODUCTION

Throughout the life of individuals, different mutational processes occur that leave characteristic patterns in tumors, called mutational signatures. One of the causes are alkylating agents, to which we are constantly exposed.

From the detection of these signatures, it is possible to infer the etiology of cancers. Thus, studying them in research and even in clinical practice is a novel field with great applicability in the near future.

METHODOLOGY

An advanced bibliographic search has been made in Google Scholar and PubMed databases with different combination of the terms "mutational signatures", "cancer", "alkylating agents", "software" and related using Boolean operators.

The results have been sorted by date –last 10 years– and by the impact factor of the journal. Review articles have been first selected, and then specific experimental articles have been included for their relevance.

OBJECTIVES

Define the concepts of *mutational signatures* and *alkylating agents* and compare the software available to decipher mutational signatures characteristic of cancers caused by alkylating agents. Finally, to explain which signatures have been identified and to study whether there is a relationship between them and any specific cancer.

RESULTS

1.

Mutational signatures are **unique patterns of mutations** present in the cancer genome generated by multiple mutational processes occurring throughout life –with variable strengths and durations– (Fig. 1).

Types of mutational signatures

SBS DBS ID

2.

Software powerful enough to decipher these signatures are needed. Therefore, musicatk [2] was developed, which combines several functions and allows comparison with the Catalogue of Somatic Mutations in Cancer (**COSMIC**) database [3], where all currently identified mutational signatures are collected.

3.

Alkylating agents are highly reactive chemicals with mutagenic, carcinogenic, teratogenic and immunosuppressive actions that add alkyl groups directly onto the guanine base of DNA. This results in the formation of cross-bridges between the strands leading to **inhibition of cellular processes, DNA fragmentation or apoptosis**. The guanine base can also mispair with a thymine instead of a cytosine and cause **mutations**.

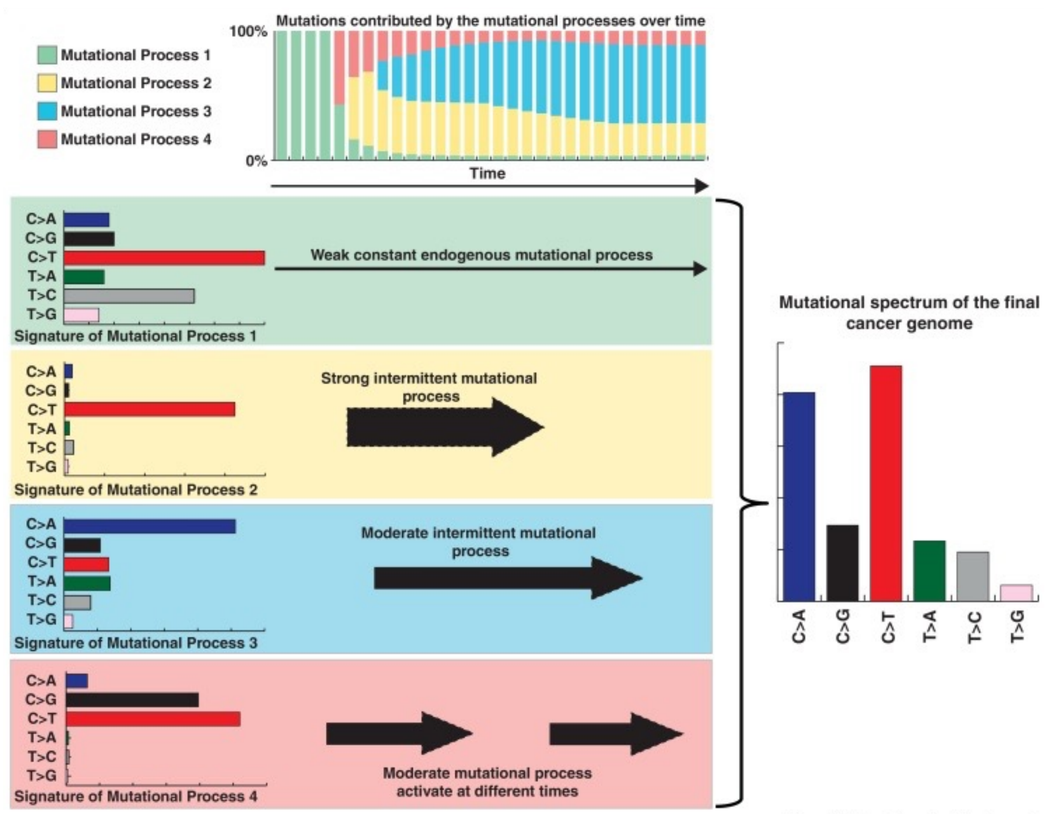

Fig. 1. *Mutational processes operative in a cancer. Extracted from Alexandrov and Stratton [1].*

4.

Currently, there are two identified signatures caused by alkylating agents: SBS11 and SBS90 signatures (Fig. 2).

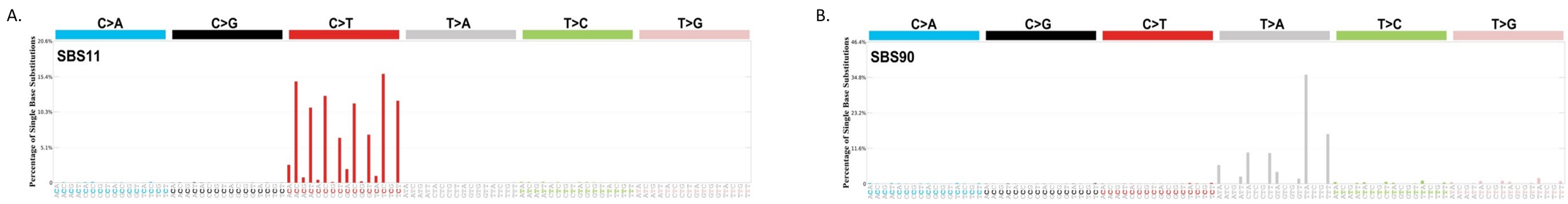

Fig. 2. *SBS signatures caused by alkylating agents. A) SBS11 signature associated to temozolomide. B) SBS90 signature associated to duocarmycin exposure. Extracted from COSMIC database [3].*

5.

To date, no specific cancers directly caused by exposure to alkylating agents have been characterized. The identified mutational signatures associated with these agents are from cancers that recur after treatment with alkylating agents. For example, the SBS-MM1 signature (Fig. 3) is associated with melphalan exposure in multiple myeloma relapses.

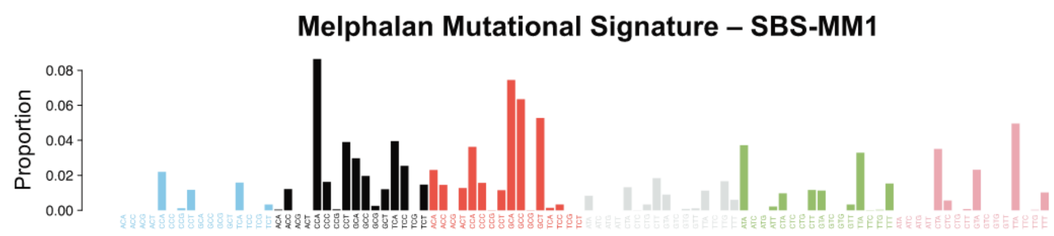

Fig. 4. *Malphalan Mutational Signature (SBS-MM1). Extracted from Maura et al. [4].*

CONCLUSIONS

- Identifying mutational signatures in human cancer has great applicability in both research and clinical practice to understand the etiology of cancers, as well as helping us in their prediction and prevention.
- Software to extract signatures are constantly adapted and improved as new factors that affect mutational signatures are discovered.
- One of the agents we are constantly exposed to are alkylating agents, which can be used as an antitumor therapy but are also mutagenic and carcinogenic.
- Currently, some signatures associated with alkylating agents have been characterized in recurrent tumors, but no signatures have been detected in *de novo* cancers caused by exposure to these agents.
- Therefore, many signatures remain to be discovered, and further experimental studies testing different alkylating agents and studying the downstream effects are needed.

References

1. Alexandrov LB, Stratton MR. Mutational signatures: the patterns of somatic mutations hidden in cancer genomes. *Curr Opin Genet Dev* 2014; 24: 52–60.
2. Chevalier A, Yang S, Khurshid Z, et al. The Mutational Signature Comprehensive Analysis Toolkit (musicatk) for the Discovery, Prediction, and Exploration of Mutational Signatures. *Cancer Res* 2021; 81: 5813–5817.
3. Cosmic. COSMIC - Catalogue of Somatic Mutations in Cancer [Internet]. 2021 March [accessed 22 November 2021]. Available at: *https://cancer.sanger.ac.uk/cosmic.*
4. Maura F, Weinhold N, Diamond B, et al. The mutagenic impact of melphalan in multiple myeloma. *Leukemia* 2021; 35: 2145–2150.
5. Alexandrov LB, Kim J, Haradhvala NJ, et al. The repertoire of mutational signatures in human cancer. *Nature* 2020; 578: 94–101.
6. Kucab JE, Zou X, Morganella S, et al. A Compendium of Mutational Signatures of Environmental Agents. *Cell* 2019; 177: 821-836.e16.

UAB Universitat Autònoma de Barcelona