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Opinion

Hypothetical role of RNA damage avoidance in preventing human disease

Damien Brégeon, Alain Sarasin *

Institut Gustave Roussy PR2, CNRS UPR-2169, 39 rue Camille Desmoulins 94805 Villejuif Cedex, France

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Abstract

Most of nucleic acids damaging agents are not only restricted to DNA but equally affect DNA and RNA molecules. Considering that RNA damage could be very toxic for the cell, a property used by some cancer treatments, it would not be unexpected to find out that several proteins may be involved in RNA damage avoidance mechanisms helping cells to counteract such cytotoxic effects. Up to now, only one specific repair mechanism allowing cells to deal with toxic effects of methylated RNA have been described. However, there are in the literature several data suggesting that this study may only be the tip of the iceberg and that cells might be able to counteract the deleterious effects of a large variety of RNA damage. In this review, we will discuss the different proteins that may be involved in the mechanism of RNA damage avoidance and their potential role in human diseases.

Keywords: RNA lesions; RNA repair; Cell death; Cancer

Prologue: Dangerous skiing with Phil

I (Alain) arrived in Phil's lab on a September 4th, which was Labor Day! I joined his laboratory to work on aflatoxin B1 (that was and still is the most potent carcinogen for humans) and on the repair of its lesions in xeroderma pigmentosum cells as well as to study SOS-like repair pathway in human cells using the SV40 virus as a molecular probe. The whole laboratory was not very keen on seeing some French guy manipulating chemical carcinogens as well virus able to infect humans in a laboratory essentially used to study UV light. However, Phil's kindness and his scientific vision of the future rendered him very reactive to my projects and he allowed me to develop the research projects I had planned.

In the course of my first winter at Stanford, I discovered that Phil and I shared another passion that is going down the snowed slopes in the Californian Sierra Nevada Mountains. Our two families spent several weekends in a nice Northstar condominium. Phil is a very good skier (see Fig. 1), his father being a ski manufacturer. One day we were going up on a ski lift at the Olympic Squaw Valley Resort and were discussing

* Corresponding author. Tel.: +33 1 42 11 63 28; fax: +33 1 42 11 50 08.
E-mail address: sarasin@igr.fr (A. Sarasin).

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Fig. 1. On top — Phil in the French Alps.

a new experimental assay while mid-way up-hill, we arrived at the mid-station where Phil, for no reason, got out of the lift. Very surprised of course, I did exactly the same although this place was not supposed to be skied by "normal skiers" and probably closed to the public. It was, indeed, the starting point of the famous K2 downhill slope of the VIIIth Olympic Winter games. Once the surprise to be on this location was passed, we tried to examine the situation he put us in. We were at the edge of a steep incline, "only" 45°, that looked to us as a 90° angle, started from 8200 ft down to 6500, and completely icy, because it was facing full north, and full of bumps. At that point, we did not talk too much but we knew very well, both of us, that the first mistake would let us go directly from the top to the bottom without any possible stop and eventually leading to a wheelchair at the best. Without any choice, we started slowly downhill hoping to make easy turns at each icy side of the slope. Fortunately, after a few turns and moments of pure panic we did make it to the bottom of the K2 with no fatal mistake although it took us nearly half an hour. Interestingly, the winner of the men's downhill Olympic games was a French skier, Jean VUARNET, with a 2 min and 6 s time! Fortunately, we did ski several times together at several other locations with no other major problems. But I am careful now not to have too serious scientific discussions while being outside on the chairlift. Not only for skiing, but of course also for science and his humanism, I would very much like to thank Phil for his friendship and the enlightened vision of science he shared so spontaneously with me.

1. Introduction

Nucleic acids of all organisms are continuously damaged by extrinsic and intrinsic physical and chemical agents. It is well documented that damage to DNA could be very harmful for all cells and is the source of several consequences such as cancer development, apoptosis or genetic diseases. Nonetheless, DNA is not the only target for deleterious nucleic acids damaging agents, such as alkylating agents, reactive oxygen species (ROS) and UV-radiations, since RNA molecules may also be affected by those agents as well. Furthermore, since RNA is mostly single-stranded, it may be more susceptible to damaging agents than DNA, whose bases are protected by hydrogen bonding and located inside the double helix. In this view, it is highly probable that significant damage to RNA occurs when cells are exposed to nucleic acids damaging agents. Consequences of RNA damage on cell physiology may be different depending on the type of the RNA lesion considered. As for DNA lesions, some of the RNA lesions may have altered pairing capacity and thus be at the origin of erroneous protein production (Fig. 2). For example, the mutagenic 5-fluorouracil can be incorporated into newly synthesized RNA molecules which might lead to cytotoxic erroneous protein synthesis [1,2]. In the case of bulky RNA lesions, the translation machinery may be inhibited and thus lead to cell death. For example, cisplatin-induced translation inhibition is due to the crosslinking of RNA molecules to themselves [3]. This inhibition may contribute to the cytotoxic effect of cisplatin and to the cancer cell death.

It is usually considered that, in a cell, RNA is more abundant than DNA. Moreover, almost all of the cellular RNA have indeed functional capacity for protein