

Les mardis de
L'IAB

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**RNA DAMAGE - MORE THAN JUST A CANARY IN THE
COAL MINE**

19. SEPTEMBER 2023 – 11 AM – LECTURE HALL

Alkylating agents are well-established chemotherapy agents used for multiple types of cancer. These agents induce various types of adducts in both DNA and RNA, with the simplest being the addition of a methyl group. The toxic effects of DNA alkylation and its repair pathways have been well-studied. However, the functional consequences of RNA damage in cells are poorly understood. We previously revealed that aberrant RNA methylation can trigger a DNA repair pathway specific to alkylation damage, suggesting that these alkylation-induced RNA adducts could be recognized and contribute to cellular signaling responses. Here, we show that an epitranscriptomic reader, YTHDC1, promotes genome integrity due to alkylation damage through a direct interaction with methylated RNAs. Using various in vitro and cell-based approaches, we show that YTHDC1 binds to N1-methyladenosine (m1A)-containing RNAs upon alkylation, in contrast to its established binding to N6-methyladenosine (m6A)-containing RNAs under physiological conditions. Functionally, we find that YTHDC1 promotes alkylation resistance at least partly through R-loop formation, as its loss can be rescued by expressing nuclear RNase H1. Strikingly, countering m1A formation using an RNA-specific demethylase can also rescue alkylation sensitivity, DNA break formation, as well as R-loop accumulation in YTHDC1-depleted cells. These results indicate that human cells have an unappreciated mechanism to counteract damaged nuclear RNAs, which may otherwise contribute to DNA damage genomic instability.

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Allée des Alpes, 38700 La Tronche (tram line B, stop : Grand Sablon)
The seminar is followed by discussions and exchanges with the speaker and a sandwich buffet is offered