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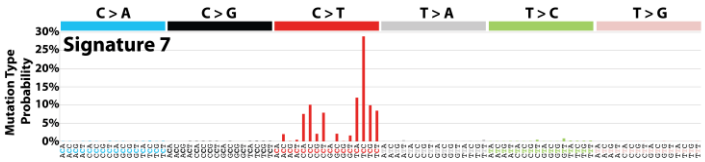
Mutational footprints and mutational toxicity of chemotherapies

DNA damage can be generated by different causes, and it can be repaired by different methods. This repairment is what can cause mutations in DNA.

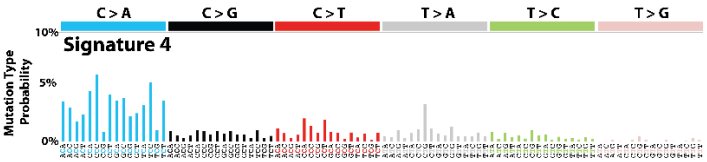
Having one of these mutations doesn't necessarily mean that cell is going to develop into a tumor. Tumors have thousands of mutations in their cells: they have specific somatic mutations that can be found in these tumor cells, and not in the rest of the body. Healthy cells can have mutations too, even thousands of them, but the place and type of mutation is what's going to determine if a cell is going to develop a tumor or not.

There are a few specific mutations known for being related with cancer in general, or with specific types of cancer. The different causes of DNA damage cause different types of mutations: this is what's been called **mutational signatures**. An example of this is the mutations caused by UV light (signature 7):



Ultraviolet exposure causes, mainly, C > T mutations. This mutational signature is found in great measure in melanoma patients, as it is mostly caused by this type of exposure.

Another widely known mutational signature is the tobacco exposure signature (signature 4):



The way these mutations are caused is as follows: first, there's a DNA lesion. The cell will try to repair the damage, and will either be able to repair it or not. This repairment is what will generate the mutations, and when the cell tries to replicate it will spread this mutation.

There are factors than can make a region more prone to mutations: for example, it's been found that if there's a protein bound to a DNA region (for example, a transcription factor), it increases 5-fold the number of mutations in that region. This is what occurs in gene promotors. This union, for some reason, interferes with reparation.

For similar reasons, it's been found that there's more mutations in nucleosomes, and less in the linker DNA. If we analyze the way the DNA is wrapped around the histones, we can see how the minor-in is touching the nucleosome, and the minor-out is facing outwards, away from the nucleosome. In different types of cancer there's mutations in a different area: in esophagus cancer, most mutations are in the minor-in, and in melanomas most are in the minor-out.

This could be explained by the damage generation: in the ones we have information on (damage maps), like UV light, we know the damage is periodic. This way, the damage is always in the same area, the minor-out. We know repair mistakes are also periodic, so if we take this two things we can see why mutations are periodic, too. We find this periodicity in all eukaryotes.

Most germline mutations are C > T. We know most minor groove-in mutations are A > T, and most major groove-out mutations are G > C. They think that it's because this causes a better bending of DNA.

Chemotherapy has many side effects, it's a source of DNA damage too, so it has a mutational footprint. After treatment, some cells die, and others generate mutations. We can't see exactly which mutations it's caused, unless there's a metastasis.

What's specially interesting, then, is identifying the mutational footprints of cancer therapy.