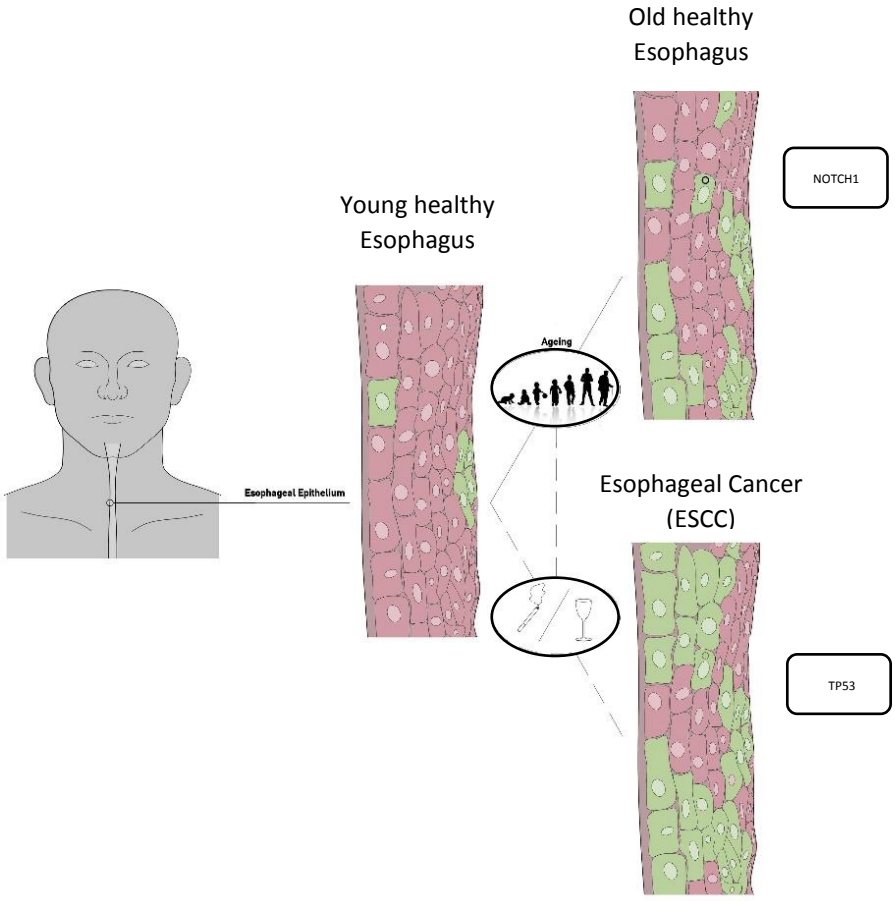
The ultimate oxymoron:
Cancer Mutations in Normal Esophageal Epithelia



Esophageal cancer occurs when cancer cells develop in the esophagus, a tube-like structure that runs from our throat to our stomach. There are two main types of esophageal cancer, squamous cell carcinoma (ESCC) and adenocarcinoma.

A group of scientists studied the mutations that arise in esophageal tissue during healthy ageing and compared these with changes that occur in ESCC (Yokoyama et.al, 2019). More precisely, the authors analyzed samples of healthy and cancerous esophageal tissue from individuals with differences in age and risk of developing ESCC. Heavy alcohol drinkers and/or smokers were classified as a group of high risk. It is worthy to mention that in Japan, which was the main tank of samples, most esophageal cancers are squamous-cell carcinomas.

In order to investigate variations in the genome of donors, different sequencing methods were used, such as whole genome (WGS) and whole exome sequencing (WES), as well as deep targeted sequencing of 24 genes. In contrary to WGS that defines the sequence of DNA genome wide, application of WES is able to decode

only the sequence of the exons, while the deep targeted sequencing is a high-coverage DNA sequencing of selected genes.

Surprisingly, they found mutations in cancer associated genes, not only in cancer samples, but also in those from healthy individuals. Moreover, the total burden of mutations was in linearity with ageing. Thence, the accumulation of driver mutations per se is not the main event that leads to cancer progression. Other co-factors, like tobacco and alcohol (lifestyle risks) may lead, to transformation of normal esophageal epithelium to esophageal cancer, as well. The patterns of mutations were analyzed to decode the underlying mechanisms of mutational processes and in total 4 mutational signatures were identified, with the most common mutation to be, a C to T transition at a CpG context. As far as the mutations of longer size (amplifications or deletions with a length more than 1kb), the cancer samples exhibit higher number comparing to samples from healthy individuals.

Furthermore, the group showed that the most commonly mutated genes in cancerous and healthy samples are TP53 and NOTCH1, respectively. In fact, the TP53 gene is the most frequently mutated gene in human cancer, indicating that it plays a substantial role in preventing cancer formation. On the other hand Notch1 plays a key role in cell growth and division, differentiation and apoptosis, as well as in cell fate determination.

In conclusion, during ageing process cancer-associated mutations are accumulated in such a way that can cause even the complete remodelling of the esophageal epithelium. Additionally, presence of co-factors such as tobacco or alcohol increase the number of mutations by accelerating the mutagenesis process.

The next step in order to further investigate the causes of ESCC, is to study individuals coming from various locations because normally there are crucial differences in the frequency and the lifestyle risks of ESSC. Regions of high incidence include Eastern to Central Asia, South Africa and South America, whereas low levels of ESCC are presented in Western world.

Finally, another future goal could be to determine mutations that appear in healthy cells and relate them with other chronic diseases associated with ageing. This could be ideally used for the creation of mutagenesis map of healthy tissues, that would be a very useful tool for early diagnosis and targeted therapy.