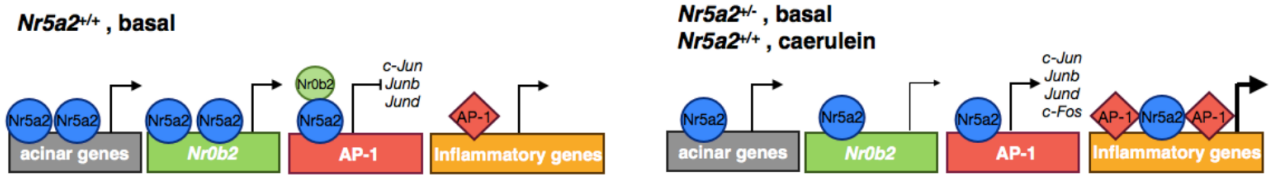
NR5A2 – What does not differentiate us may hurt us

Ana Oliveira, **Andreia Silva**, André Barros, Joana Bugalhão, Patrícia Apura



Nowadays, it is still thought that tissue-specific differentiation pathways and inflammatory programs work separately. In the pancreas, a heterozygous genotype of the receptor Nr5a2, a key regulator in a variety of metabolic processes as well as pancreatic development and differentiation, allows for a normal and functional pancreas; however, it is also associated with a hindered regeneration after mild inflammatory stimulus and with an increased risk of pancreatic ductal adenocarcinoma (PDAC). Using a combination of mouse and human data the authors try to understand how the *Nr5a2* regulator promote this inflammatory state.

Cobo *et al* found an association of low NR5A2 protein levels with PDAC susceptibility in pancreatitis patients, which further motivated them to investigate a possible causal relationship of this receptor on sensitivity to inflammation and, indirectly, adenocarcinoma development. Interestingly, heterozygous *Nr5a2*$^{+/-}$ mice show decreased protein levels similar to the ones of pancreatitis patients. Since they have a similar inflammatory gene expression profile, mainly for up-regulated genes, it is clear that Nr5a2$^{+/-}$ mice is indeed a good animal model to study the relationship between *Nr5a2* genotype, expression, and cancer risk.

Despite being histologically normal, *Nr5a2*$^{+/-}$ mice have impaired pancreatic regeneration capabilities. As such, they hypothesized that a subtle defect might exist in basal conditions and to test it RNA-seq was used to compare the transcriptomes of *Nr5a2*$^{+/+}$ and *Nr5a2*$^{+/-}$ pancreata. This data showed an association between the *Nr5a2*$^{+/-}$ genotype and the expression of inflammatory genes that is mediated by important transcription factors related with these responses, such as AP-1. This genotype can indeed increase the expression of the genes of AP-1 protein family members (mainly c-Jun) and increase their affinity to the promoters of pre-inflammatory genes. This leads to a basal inflammatory state that has a similar transcriptional profile as the one of a wild type after a mild stimulus of acute pancreatitis (via injection of caerulein). However, concerning gene expression, the individuals with *Nr5a2*$^{+/-}$ genotype respond in a similar way to the wild type. A long-term consequence is the fact that the inflammatory response, via AP-1 proteins, remains active only in *Nr5a2*$^{+/-}$ genotype after 24h of the stimulus, which can be a signal of reduced ability for inflammation resolution and, thus, open new avenues for further work on the topic.

In order to understand the mechanisms responsible for the basal pre-inflammatory state of *Nr5a2*$^{+/-}$ pancreata, they used Nr5A2 Chip-qPCR and observed a relocation of Nr5a2 binding from the promoters of pancreas genes to the promoters of inflammatory genes. This effect was called “the Nr5a2 transcriptional switch”. Most importantly, this is also true for wild type mice after induction.

It was shown that c-Jun and Nr5a2 are part of the same complex in inflammatory states and may be involved in the transcriptional switch engaged by Nr5A2. Indeed, deletion of c-Jun abolished the up-regulation of AP-1 components and inflammatory genes, and also limits the abnormal response to induction of acute pancreatitis, restoring a phenotype more characteristic of Nr5a2 homozygous mice. Additionally, Nr5a2 can modulate AP-1 gene expression due to the down-regulation of its co-repressor, Nr0b2.

These results show that transcriptional networks involved in homeostasis can also, under genetic constraints, trigger inflammation. Transcriptomic variation deserve more attention and may, more accurately, reflect and justify the susceptibility to disease than genomic variation. In that sense, more work it still needed to verify if, in *Nr5a2*$^{+/-}$ pancreas, oncogenes are differentially expressed, explaining the association of less expression of Nr5a2 with preneoplastic lesions and pancreatic ductal adenocarcinomadescribed in humans.