HUMAN GENETICS GROUP

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OVERVIEW

We have continued to decipher the genetic bases of hereditary and sporadic breast cancer. In addition, we participated in a project that combines the genotype and the phenotype in order to stratify and select women at high risk of developing breast cancer. Other families with rare tumours are also the object of our studies, for example, testicular cancer whose genetic bases are unknown. More recently, we started working on a study to elucidate the common genetic origin of different autoimmune-originated pathologies: gastric neuroendocrine tumours or chronic atrophic gastritis plus different immune diseases in other tissues, such as thyroiditis, diabetes or arthritis. We have identified several genes thereby opening up new avenues for new treatments. Finally, we have progressed in understanding the role of glycosylase genes as modifiers of hereditary breast cancer and their role along the cell cycle.

"We have discovered 3 new genes that confer susceptibility to testicular cancer and a moderate breast cancer susceptibility gene. A whole pathway with several genes associated to gastric neuroendocrine tumours or chronic atrophic gastritis plus several immune diseases, has been identified."

RESEARCH HIGHLIGHTS

Deciphering the role of rare variants in breast cancer

The European project BRIDGES, in which we participate, has 3 main phases. The first one was the study of 36 candidate genes in 60,000 breast cancer cases and controls in order to determine their role as possible moderate susceptibility genes. This part of the work has been completed and we have confirmed 20% of them. The second phase will involve the whole sequencing of these 60,000 cases, trying to discover new susceptibility genes. The work will start towards the end of year or the beginning of next year; our group will be responsible for coordinating this Work Package.

Breast cancer susceptibility genes

In a whole-exome sequencing study of 4 BRCAX families we identified a mutation in the moderate susceptibility gene *ATM* as being responsible for the disease in one of the families (Tavera-Tapia *et al.*, 2017). In a second family, we found a deleterious mutation in an excellent candidate gene *RECQL5* that belongs to a family of DNA helicases that have a role in the Homologous Recombination (HR) DNA repair pathway. Using a combination of targeted next-generation sequencing and genetic and functional assays, we identified 7 deleterious or likely deleterious mutations in the gene in a series of 700 BRCAX cases and only 1 deleterious mutation in 700 controls, suggesting that the gene could actually explain a small percentage of the BRCAX families (Tavera-Tapia *et al.*, submitted).

SNPs and the BER pathway

We investigated the molecular basis underlying the effect of an SNP in the DNA glycosylase *UNG* as an ovarian cancer risk modifier in *BRCA2* mutation carriers (Baquero *et al.*, submitted). We found that an SNP rs34259 is associated with significant UNG down-regulation and a better performance of the enzyme, measured by a lower accumulation of uracil at the telomeres in *BRCA2* mutation carriers. Our findings could help to explain the association of this variant with a lower cancer risk in *BRCA2* mutation carriers. In addition, we want to study the role of this and 2 other glycosylases previously studied, OGG1 and NEIL2, across the cell cycle.

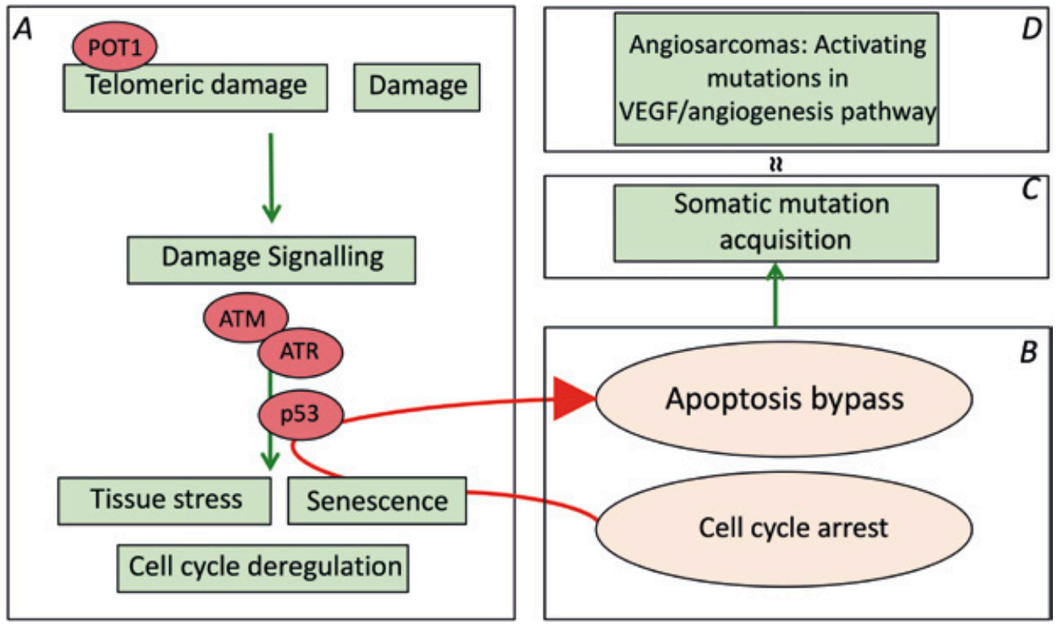

Figure Tumorigenic mechanisms for cardiac angiosarcomas (CAS). (**A**) Mutations found in *POT1* and other genes involved in the damage response signalling (*ATR/ATM* and *TP53*), correlate with the constitutional deregulation of the cell cycle, which triggers senescence and tissue stress due to the depletion of the progenitor cells. (**B**) Malfunction of the tissue stress would arise a bypass in the apoptotic regulation. (**C**) Apoptosis bypass would fuel the acquisition of multiple somatic events. (**D**) In all the studied CAS (familial – carrying POT1 mutation – and sporadic CAS), somatic activating mutations were found in the angiogenesis pathway, which drives tumour formation.

Familial cancer exome project

In 2015, we identified a gene responsible for families with cardiac tumours (*POT1*) (Calvete *et al.*, 2015). Recently, we described its relation not only to cardiac tumours but also to other different types of tumours (Calvete *et al.*, 2016). We investigated why the malfunction of this gene involves not only abnormal telomere length but is also able to generate different tumours in different tissues in a similar way as P53. We analysed the somatic changes in several cardiac tumours with and without *POT* mutations and have concluded that the inhibition of *POT1* gene function, and the damage-response malfunction, would activate ATR-dependent DNA damage signalling, which increases cell cycle arrest in asymptomatic tissues and might interfere the apoptosis mechanism; this would permit the further acquisition of somatic mutations in the VEGF/angiogenesis pathway (POT1 deregulation) and other angiosarcomas (mutations in damage-signalling), which drives tumour formation. The same observation was made in sporadic cardiac lesions (Calvete *et al.*, submitted).

In 2015, we published the identification of the *ATP4A* gene as being responsible for families with gastric neuroendocrine tumours (Calvete *et al.*, 2015). In 2017, we extended this study to a new family that presented the same lesion along with hypothyroidism and arthritis. The family presented 2 mutations in *ATP4A* and *PTHR1* in a digenic model (Calvete *et al.*, 2017). We further explored the apparent relation of gastric autoimmune disease (gastric neuroendocrine tumour or chronic atrophic gastritis) plus a second immune disease; we found several mutations in new genes involved in homeostasis function (solute carriers) altering *ATP4A* function. We have designed a panel of 15 genes from this pathway and we are currently performing a screening in a large number of patients carrying these combinations. Several gastroenterologists, pathologists and endocrinologists are collaborating in this project.

During the past few years, we have been collecting families with testicular cancer and also sporadic tumours. We conducted a first study in 17 families with over 71 members and by whole exome sequencing we identified several candidate genes; 3 of them (PLEC, EXO5 and DNAH7) were validated in a large case-control association study (Paumard *et al.*, 2018). We then continued the study with more cases and separated 2 main histologic groups, seminomas and non-seminomas. We differentiated several altered pathways and the spermatogenesis pathway was significantly altered. We studied this pathway in depth and discovered a biomarker that differentiated familial, bilateral and sporadic cases, as well as seminomas from non-seminomas. ■

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