Our work focuses on deciphering the genetic bases of hereditary and sporadic breast and ovarian cancer and other rare tumours. During 2020, we contributed to the definition of the main bona-fide breast cancer (BC) susceptibility genes through our substantial participation in an ambitious international collaboration (BRIDGES, a European project). In addition, we obtained funding to develop two new projects focussed on breast and ovarian cancer genetics. We have also been exploring the currently unknown genetic basis of testicular cancer. More recently, we started a study to elucidate the common genetic origin of different autoimmune endocrinopathies, such as chronic gastritis atrophy, thyroiditis, diabetes, or arthritis, and we identified several genes that open a new scenario for diagnosis and treatment. Finally, we found interesting results suggesting a synthetic lethal interaction between BRCA1 and OGG1 and a synergistic effect between OGG1 and PARP1 inhibitors.

“...In 2020, we contributed to determining the most relevant genes in BC susceptibility, we found several candidate genes explaining the possible common origin of autoimmune endocrinopathies, and we identified a synergistic effect between OGG1 inhibitors and PARP1 inhibitors.”

RESEARCH HIGHLIGHTS

Hereditary breast and ovarian cancer

Deciphering the role of rare variants in BC

The first publication reporting results obtained by the European project BRIDGES, to which we made a major contribution, was released this year. Thirty-four confirmed or putative BC susceptibility genes were sequenced in 60,466 cases and 53,461 controls. Nine genes were confirmed as bona-fide BC susceptibility genes, and the risk conferred by their mutations to develop the disease was refined. These results, published in the New England Journal of Medicine (Dorling et al., 2020), are highly relevant to improving the genetic diagnosis, counselling and follow-up of BC patients and their families. In addition, we participated in the largest collaborative international study evaluating the risk conferred by mutations in the RAD51C and RAD51D genes to develop breast and ovarian cancer (Yang et al., 2020).

Identification of 14 new candidate BC susceptibility genes

As a complementary approach to the large collaborative projects, we are conducting a study using next-generation sequencing (NGS) technologies in a few, very well selected families, to identify new BC susceptibility genes. This approach led to the identification of RECQL5, a member of the RECQL-helicases family, as a new BC susceptibility candidate (Tavera-Tapia et al., 2019). Besides RECQL5, we identified 13 additional candidate genes that are extremely interesting because of their function, the potential deleteriousness of the variants, and their rarity in the general population. We developed an NGS panel containing this set of genes and will evaluate their role in BC by sequencing a large set of 3000 Spanish BC families.

Modifier genes in BRCA1/2 genes

We continue to play an active role in the CIMBA consortium (Consortium of Investigators of Modifiers of BRCA1 and
Several mutations putatively affecting the cell’s internal architecture were found in other tumours, not only in primary tumours but also in other tissues (thyroid, epididymis, pancreas, skin), explaining this autoimmune polyendocrine syndrome (Calvete et al., under review).

Testicular Germ Cell Tumour (TGCT)

During the past year, we explored TGCT in familial, bilateral, and sporadic patients, by evaluating their clinical history and by identifying moderate susceptibility genes and pathways involved in the disease. Familial and bilateral patients develop TGCT significantly earlier, and their relatives have a lower percentage of other tumour types compared to sporadic patients, suggesting a more relevant genetic background in their origin. A gene ontology analysis was performed with the variants obtained by WES, and the glycosylation pathway, a post-translational modification that consists of a carbohydrate attaching to different functional groups, was found to be overrepresented in all cohorts of patients and thus might be involved in the development of the disease. In addition, the glycosylation genes with variants uncovered by WES were significantly located in the same cytophase as the susceptibility loci previously described by GWAS studies. 

BRCA2, which made important contributions in 2020 i) showing the modification of ovarian cancer risk by the FBS (Polycyclic Risk Score) in BRCA1 and BRCA2 mutation carriers (Barnes et al., 2020), ii) identifying the spectrum of mutations in male BC patients harbouring mutations in the BRCA2 genes (Silvestri et al., 2020), and iii) associating mutations in different domains of BRCA1 and BRCA2 with prostate cancer risk (Patel et al., 2020). We also started collaborating in the ambitious CONFLUENCER project, funded by the National Cancer Institute, the aim of which is to perform new Genome-Wide Association Studies (GWAS).

DNA glycosylase inhibitors as a new therapeutic approach in hereditary BC patients

In 2014, we reported that SNPs located in genes encoding for DNA glycosylases involved in the Base Excision Reparation (BER) pathway could act as breast and/or ovarian risk modifiers in BRCA1/2 mutations carriers (Osorio et al., 2014). Since then, we have been exploring the mechanisms of action of these SNPs (Benten et al., 2016; and Baquero et al., 2019, respectively) as well as of the OGGL glycosylase inhibitor THS487 and its possible therapeutic use in BC patients. We found that the inactivation of BER by THS487 increases the accumulation of oxidised bases at the telomeres, leading to telomere loss and post-mitotic defects (Baquero et al., 2020, under review) (FIGURE). Moreover, we discovered that THS487 enhances the activity of the PARPI inhibitor olaparib in BRCA1 deficient cells. These preliminary results might represent the proof-of-concept for new alternative or complementary therapies for hereditary breast and ovarian cancer patients.

Ovarian cancer

Endometrioid (EOC) and clear cell (CCOC) ovarian carcinomas are considered refractory to chemotherapy and present bad outcomes once disseminated. About 15% show defects in mismatch repair (MMR) and microsatellite instability (MSI). MMR is a predictor of immunotherapy response, and the global burden of instability has been associated with survival in other tumour types. We compiled more than 200 EOCs and CCOCs and assessed the global load of microsatellite instability and tumour mutational burden in an ad hoc designed 11-GSB ovarian cancer panel (OvaSeq-MSI). OvaSeq-MSI includes a large set of MS approaches to improve MSI determination and provides information about mutations in ovarian cancer, mosaicism, genetic susceptibility genes, or therapeutic targets. Preliminary results show a good correlation between global instability and mutation burden, and an association between the extent of both indicators and improved disease evolution in patients (lack of relapse).

Familial cancer exome project

Autoimmune polyendocrine syndrome (APS)

In 2015, we published research identifying the ATP4A gene as being responsible for families with achlorhydria-mediated gastric neuroendocrine tumors (gNET) (Calvete et al., 2015 and 2016). In 2017, we extended this study to a new NET family that presented with hypothyroidism and arthritis explained by two mutations in the ATP4A and PTTHR1 genes (Benitez et al., 2017). In addition, we explored the pathogenic mechanism underlying tumour progression mediated by mutations affecting achlorhydria (Benitez et al., 2020). We have further investigated the apparent relationship of gastric autoimmune disease (gastric neuroendocrine tumour or chronic atrophic gastritis) co-occurring with other autoimmune diseases (hypothyroidism, arthrosis, D, villitis, etc.) using a large cohort of patients.

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FIGURE

The inactivation of OGGL with THS487 inhibitor causes several mutations in the 11-GSB ovarian cancer panel (OvaSeq-MSI). OvaSeq-MSI includes a large set of MS approaches to improve MSI determination and provides information about mutations in ovarian cancer, mosaicism, genetic susceptibility genes, or therapeutic targets. Preliminary results show a good correlation between global instability and mutation burden, and an association between the extent of both indicators and improved disease evolution in patients (lack of relapse).

Alcohol consumption, cigarette smoking, and risk of breast cancer for BRCA1 and BRCA2 mutation carriers. Results from the BRCA1 and BRCA2 cohort consortium. Cancer Epidemiol Biomarkers Prev 29, 369-378.


utators (2020). Improved diagnosis of rare disease patients through systematic validation and reporting of rare variants to help improve disease prevention.

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