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P01

CANCER GENETICS

P01.001.A Hypoxia-mimetic agent DFO inhibits cancer cell proliferation and induces DNA damage

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Background/Objectives: Hypoxia is common in solid tumour microenvironments and has been associated with radiotherapy resistance and poor clinical outcomes. Replicating hypoxic conditions in vitro requires incubation at 1% O_2, 5% CO_2 and 94% N_2. This nitrogen-induced hypoxia is costly and time-consuming since it needs 24 hours to establish hypoxia. An alternative technique to replicate hypoxic conditions is the use of mimetics like deferoxamine (DFO). This molecule is an iron chelating agent that facilitates the accumulation of hypoxia-inducible factors and has been shown to induce apoptosis in breast tumor cell lines[1].

Methods: MCF7 (breast), VCAP (prostate), CAL33 (head and neck) and OVCAR-8 (ovarian) cancer cell lines were used to test the effect of DFO on proliferation using MTT and annexin-V/propidium iodide assays. DNA damage, specifically double strand break (DSB) formation, was tested by γH2AX foci quantification via immunofluorescence assays.

Results: DFO inhibited cell proliferation and apoptosis in a dose- and time-dependent manner. These effects were more marked than the one achieved through nitrogen-induced hypoxia. Additionally, DFO induces DNA damage through DSB formation.

Conclusion: Although DFO is usually used as a hypoxia-mimetic agent because it is cheaper and less time-consuming than nitrogen-induced hypoxia, our results show that it decreases cell proliferation and induces DNA damage through DSB formation. Therefore, its antitumoral effect should be further explored.

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1. Lynn, J. V. et al. The Role of Deferoxamine in Irradiated Breast Reconstruction: A Study of Oncologic Safety. Plast. Reconstr. Surg. 143, 1666–1676 (2019).

Conflict of Interest: None declared

P01.002.B Mapping of Splicing Regulatory Elements-rich intervals and identification of spliceogenic variants in ATM exon 7

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Background/Objectives: With a prevalence of approximately 1% in live births and even higher in foetuses, congenital heart disease (CHD) is the most common congenital abnormality. Pathogenic copy number variants are recognised as a prevalent and well-established genetic cause of CHD. Previous studies have highlighted the widespread adoption of chromosomal microarrays (CMA) as a first-tier genetic test for CHD. The primary outcome of this study was to determine the overall diagnostic yield of CMA, supplemented by subgroup analyses exploring patients with isolated CHD and those with both CHD and concomitant extra-cardiac congenital anomalies.

Methods: A systematic literature review was conducted in February 2024, using relevant keywords, within the PubMed database. Of the 531 identified studies, following the application of predefined inclusion and exclusion criteria, 36 were included in the proportional meta-analysis.

Results: In total, 9652 patients with CHD were included. The overall diagnostic yield of CMA was determined to be 10.6% (95% CI, 8.4%–13.2%), with a rate of 7.2% (95% CI, 5.1%–10.2%) observed among cases of isolated CHD and 17.4% (95% CI, 4.5%–48.4%) among patients presenting with both CHD and additional extra-cardiac congenital anomalies.

Conclusion: This meta-analysis provides evidence of the diagnostic efficacy of CMA in CHD and serves as a reference for expanding or replacing genetic testing with exome or genome sequencing.

Conflict of Interest: None declared

P07.057.D Losartan reduces aortic dilatation but does not affect aortic rupture force in MFS mice

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Background/Objectives: Marfan syndrome (MFS) can lead to aortic aneurysms, dissections, and ruptures. Losartan, an angiotensin-II-receptor-type-1 inhibitor, has been shown to slow down aneurysm progression in mouse models and humans with MFS. However, it remains unclear whether losartan exerts its beneficial effect by the prevention of rises in blood pressure or by improving the biomechanical integrity of the aortic wall. We have recently established an objective approach to measure the rupture force of the murine aorta, enabling to assess the effect of drug treatments on the biomechanical integrity of the aorta at individual level, even in the absence of arterial events. Here, we applied our approach to losartan-treated mice modelling MFS.

Methods: 4-week-old homozygous (*Fbn1*$^{mgR/mgR}$) and wild-type mice were treated for 4 weeks with losartan and subsequently euthanized. Per mouse, three 1.5-mm rings of the thoracic aorta were prepared, mounted on a tissue puller, and uniaxially stretched until rupture.

Results: The mortality rate of losartan-treated *Fbn1*$^{mgR/mgR}$ mice was not significantly lower than that of untreated *Fbn1*$^{mgR/mgR}$ mice during the study interval. Losartan treatment reduced aneurysm formation, but had no impact on the aortic rupture force of *Fbn1*$^{mgR/mgR}$ mice. Aortic rupture force measurement revealed the weakened thoracic aorta prior to micro- and macroscopic changes.

Conclusion: In mice modelling MFS, the thoracic aorta treated with losartan remains susceptible to rupture despite the reduction in aortic diameter. Thus, aortic rupture force beyond aortic diameter may be useful for the investigation of drug therapies in mouse models of hereditary aortic diseases.

Conflict of Interest: None declared

P07.058.A Reinterpretation of genetic testing for Cardiomyopathies: Less is more

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Background/Objectives: In the last years, the concept of reinterpretation of genetic testing has been considered as part of the diagnostic workflow. However, this process requires time, expert curators and new evidences to evaluate.

Recently, the European Society of Cardiology (ESC) published the new guidelines for the management of cardiomyopathies including a precise list of genes associated with the different phenotypes, including their level of contribution, posing a real support in the reinterpretation of variants in genes not clearly correlated with the disease.

To evaluate the impact of the new ESC indications, we reconsidered all genetic testing results performed in our Clinic in patients with confirmed or suspicious Cardiomyopathy.

Methods: From 2017 to 2023 we analyzed 296 probands for Cardiomyopathy, in particular 105 patients tested for Arrhythmogenic Cardiomyopathy (ACM), 113 for Hypertrophic Cardiomyopathy (HCM) and 78 for Dilated Cardiomyopathy (DCM), using a custom sequencing panel including 44 genes (11 genes for ACM, 34 for DCM and 29 for HCM).

Results: Comparison analysis with the genes reported from the ESC guidelines, considering only the definitive, moderate and strong genes, showed that 24 genes are not more associated with the phenotype and then not clinically actionable. In this scenario, we reconsidered 12 variants (8%), previously classified as VUS, changing the referral status of 8 patients, from uncertain to negative.

Conclusions: These results highlight the importance of the variant reinterpretation as a fundamental step of the genetic testing, posing the importance in the selection of the genes to analyse in order to improve the management of the patients.

Conflict of Interest: None declared

P07.060.C De novo variants in paediatric cardiomyopathies in a national rare disease initiative