



PROJECT

Supervisor:

Dr. Giovanni Peretto

Title:

EXPLORING THE ARRHYTHMOGENIC ROLE OF APOPTOSIS IN
INFLAMMATORY CARDIOMYOPATHY

Curriculum:

Clinical and Experimental Medicine

Link to the personal page of the
University or relevant hospital site
website:

<https://www.hsr.it>

Description of the Project (max 3,000 characters including spaces)

Background/gap of knowledge

Apoptosis is a form of genetically regulated cell death, which serves as a crucial mechanism to maintain cellular homeostasis by eliminating damaged or dangerous cells. The process involves a series of events, including chromatin condensation, cell shrinkage, and the formation of apoptotic bodies that are eventually eliminated by neighboring phagocytic cells. In recent times, apoptosis has emerged as a possible biomarker of "hot-phase" arrhythmogenic cardiomyopathy, a condition known for an increased arrhythmic burden.

Rationale and hypothesis

The role of apoptosis in promoting arrhythmias within inflammatory cardiomyopathy (Infl-CMP) remains unclear. Infl-CMP involves ongoing myocardial inflammation, which leads to ventricular dysfunction and triggers the development of arrhythmias. We hypothesize that apoptosis may participate in this process by determining the loss of cardiac tissue and disrupting electrical activity.

Objectives and specific aims

1) In the clinical setting, the primary aim is to identify a correlation between apoptosis and the occurrence of arrhythmias in patients diagnosed with Infl-CMP. For this purpose, the study will employ a retrospective cohort design, analysing clinical data, biopsy samples and arrhythmia monitoring records from patients previously diagnosed with Infl-CMP.

2) In the preclinical setting, our aim is to discover the mechanisms linking apoptosis and arrhythmogenesis in Infl-CMP on a molecular and cellular level. The study will rely on two experimental models:

- Murine model of experimental autoimmune myocarditis (EAM), which reproduces the immune-mediated mechanisms of human Infl-CMP;
- iPSCs-derived cardiomyocytes, reproducing the impact of apoptosis on cardiac electrophysiology in vitro.

This dual approach will allow the investigation of both cellular and systemic mechanisms of arrhythmogenesis and their relationship with the apoptotic process.

Expected outcomes

This study could have a significant clinical impact by improving our understanding of the possible pathophysiological role of apoptosis in the context of Infl-CMP.



On the clinical level, including apoptosis as a biomarker of increased arrhythmias could drive the arrhythmic risk stratification and the development of targeted therapeutic interventions in patients with Infi-CMP. Patients with higher levels of apoptosis, for example, might benefit from more aggressive antiarrhythmic or immunomodulatory therapy, or might be suitable for an earlier implantation of cardiac devices.

On the preclinical side, the study could lead to the identification of new molecular targets in the context of drug development, opening the doors to the search for therapeutic agents inhibiting the apoptotic pathways and potentially preventing arrhythmias at their source.

Skills that the student should acquire (max. 600 characters including spaces):

The skills to be acquired include those regarding experimental model management (EAM mouse model and iPSCs), in vivo electrophysiology (ECG recording, telemetry implantation and monitoring, programmed ventricular stimulation), and in vitro (microelectrode arrays (MEA), patch-clamp, calcium imaging, post-processing IT tools).

References (max. 15)

1. Valente M, Calabrese F, Thiene G, Angelini A, Basso C, Nava A, Rossi L. In Vivo Evidence of Apoptosis in Arrhythmogenic Right Ventricular Cardiomyopathy. ; 1998.
2. Bassetto G, Merlo M, Dal Ferro M, Setti M, Paldino A, Collesi C, Artioli R, Loffredo F, D'Elia S, Golino P, Fabris E, Bussani R, Metra M, Limongelli G, Sinagra G. Apoptosis, a useful marker in the management of hot-phase cardiomyopathy? Eur J Heart Fail. 2024;26:590–597.
3. Caforio ALP, Pankuweit S, Arbustini E, Basso C, Gimeno-Blanes J, Felix SB, Fu M, Heliö T, Heymans S, Jahns R, Klingel K, Linhart A, Maisch B, McKenna W, Mogensen J, Pinto YM, Ristic A, Schultheiss HP, Seggewiss H, Tavazzi L, Thiene G, Yilmaz A, Charron P, Elliott PM. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: A position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J. 2013;34:2636–2648.
4. Kari S, Subramanian K, Altomonte IA, Murugesan A, Yli-Harja O, Kandhavelu M. Programmed cell death detection methods: a systematic review and a categorical comparison. Apoptosis. . 2022;27:482–508.
5. Artico J, Merlo M, Delcaro G, Cannatà A, Gentile P, De Angelis G, Paldino A, Bussani R, Ferro MD, Sinagra G. Lymphocytic Myocarditis: A Genetically Predisposed Disease? J Am Coll Cardiol. 2020;75:3098–3100.
6. Baggio C, Gagno G, Porcari A, Paldino A, Artico J, Castrichini M, Dal Ferro M, Bussani R, Merlo M. Myocarditis: Which Role for Genetics? Curr Cardiol Rep. 2021;23. doi:10.1007/S11886-021-01492-5
7. Cannata A, Artico J, Gentile P, Merlo M, Sinagra G. Myocarditis evolving in cardiomyopathy: when genetics and offending causes work together. Eur Heart J Suppl. 2019;21:B90–B95.
8. Peretto G, Casella M, Merlo M, Benedetti S, Rizzo S, Cappelletto C, Di Resta C, Compagnucci P, De Gaspari M, Dello Russo A, Casari G, Basso C, Sala S, Sinagra G, Della Bella P, Cooper LT. Inflammation



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**APPLICATION TO ACT AS SUPERVISOR
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on Endomyocardial Biopsy Predicts Risk of MACE in Undefined Left Ventricular Arrhythmogenic Cardiomyopathy. *JACC Clin Electrophysiol.* 2023;9:951–961.

9. Austin KM, Trembley MA, Chandler SF, Sanders SP, Saffitz JE, Abrams DJ, Pu WT. Molecular mechanisms of arrhythmogenic cardiomyopathy. *Nat Rev Cardiol.* . 2019;16:519–537.

10. Mallat Z, Tedgui A, Fontaliran F, Frank R, Durigon M, Fontaine G. Evidence of apoptosis in arrhythmogenic right ventricular dysplasia. *N Engl J Med.* 1996;335:1190–1197.

11. Kavantzias N, Lazaris A, Agapitos E, Nanas J, Davaris P. Histological assessment of apoptotic cell death in cardiomyopathies - PubMed. *Pathology.* 2000. Available at <https://pubmed.ncbi.nlm.nih.gov/10968390/>. Accessed October 24, 2024.

12. Caspi O, Huber I, Gepstein A, Arbel G, Maizels L, Boulos M, Gepstein L. Modeling of arrhythmogenic right ventricular cardiomyopathy with human induced pluripotent stem cells. *Circ Cardiovasc Genet.* 2013;6:557–568.

13. Lyon RC, Mezzano V, Wright AT, Pfeiffer E, Chuang J, Banares K, Castaneda A, Ouyang K, Cui L, Contu R, Gu Y, Evans SM, Omens JH, Peterson KL, McCulloch AD, Sheikh F. Connexin defects underlie arrhythmogenic right ventricular cardiomyopathy in a novel mouse model. *Hum Mol Genet.* 2014;23:1134–1150.

14. Yang Z, Bowles NE, Scherer SE, Taylor MD, Kearney DL, Ge S, Nadvoretzkiy V V., DeFreitas G, Carabello B, Brandon LI, Godsel LM, Green KJ, Saffitz JE, Li H, Danieli GA, Calkins H, Marcus F, Towbin JA. Desmosomal dysfunction due to mutations in desmoplakin causes arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Circ Res.* 2006;99:646–655.

15. Li D, Liu Y, Maruyama M, Zhu W, Chen H, Zhang W, Reuter S, Lin SF, Haneline LS, Field LJ, Chen PS, Shou W. Restrictive loss of plakoglobin in cardiomyocytes leads to arrhythmogenic cardiomyopathy. *Hum Mol Genet.* 2011;20:4582–4596.