UNIVERSITÀ DEGLI STUDI DI NAPOLI FEDERICO II

SOCIETÀ ITALIANA DI GERONTOLOGIA E GERIATRIA

64° CONGRESSO NAZIONALE SIGG

Continuità di affetti, continuità di cure

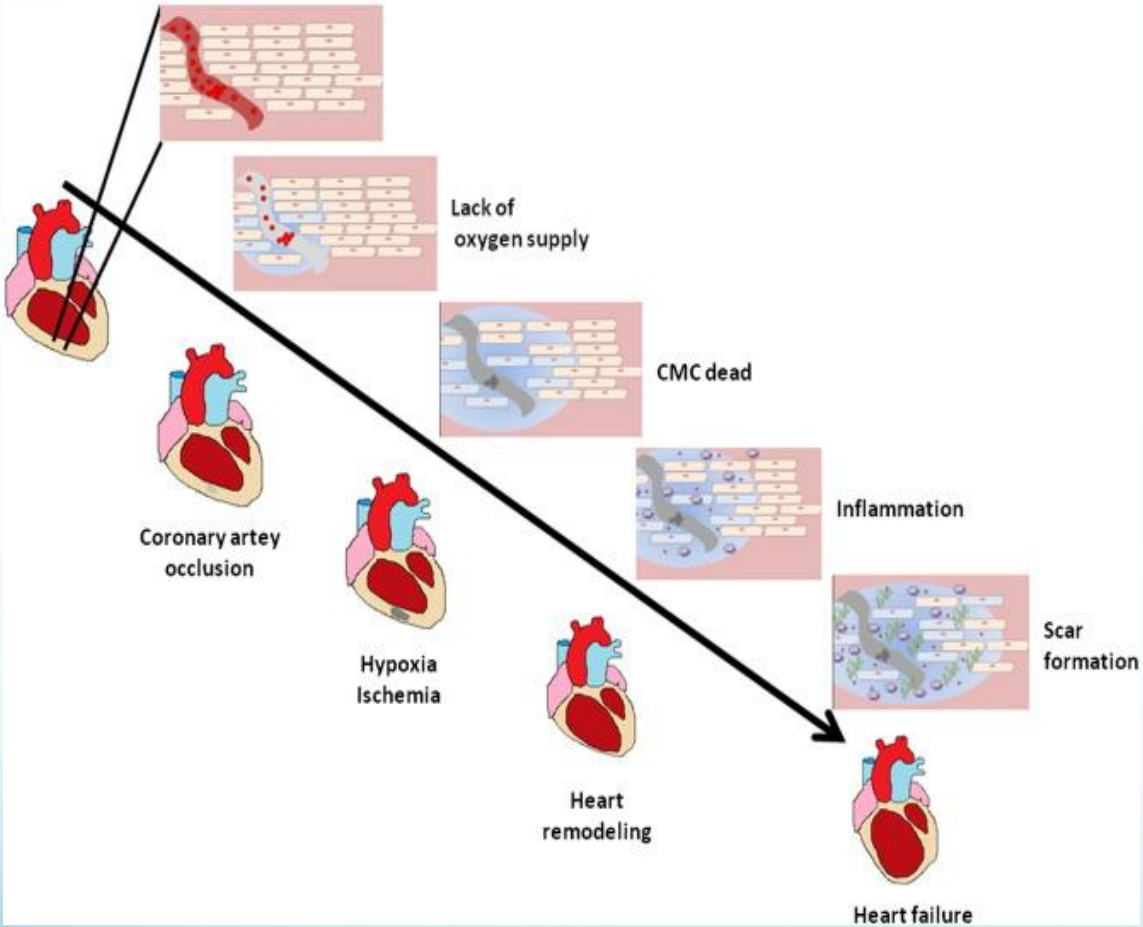
ROMA, 27/30 NOVEMBRE 2019 - AUDITORIUM DELLA TECNICA

Ruolo del metabolismo e della proliferazione cellulare nelle cardiopatie dell'anziano

Daniela Liccardo, PhD

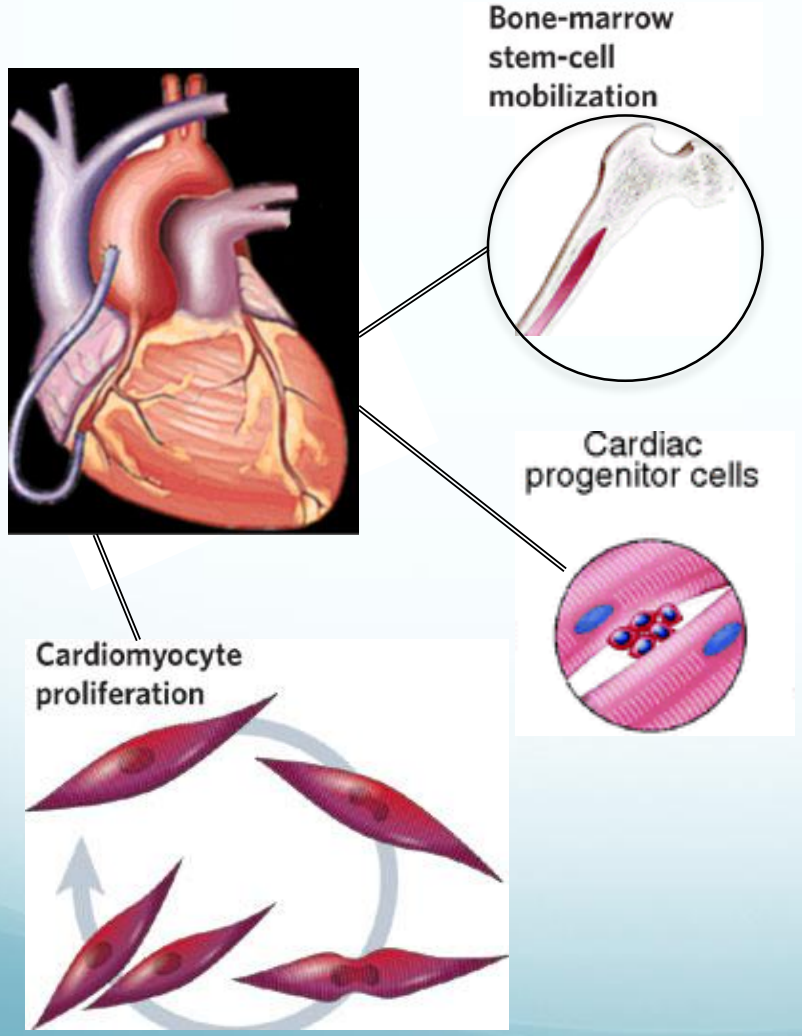
Dipartimento di Scienze Mediche Traslazionali
Universita' degli studi di Napoli "Federico II"

Heart injury and regeneration



- **Myocardial infarction (MI) remains the most common cause of heart failure**
- **The adult heart regeneration rate is not sufficient to replace lost cardiomyocytes**
- **Dead cardiomyocyte are gradually replaced by fibroblasts**

Heart injury and regeneration



Strategies to regenerate Heart:

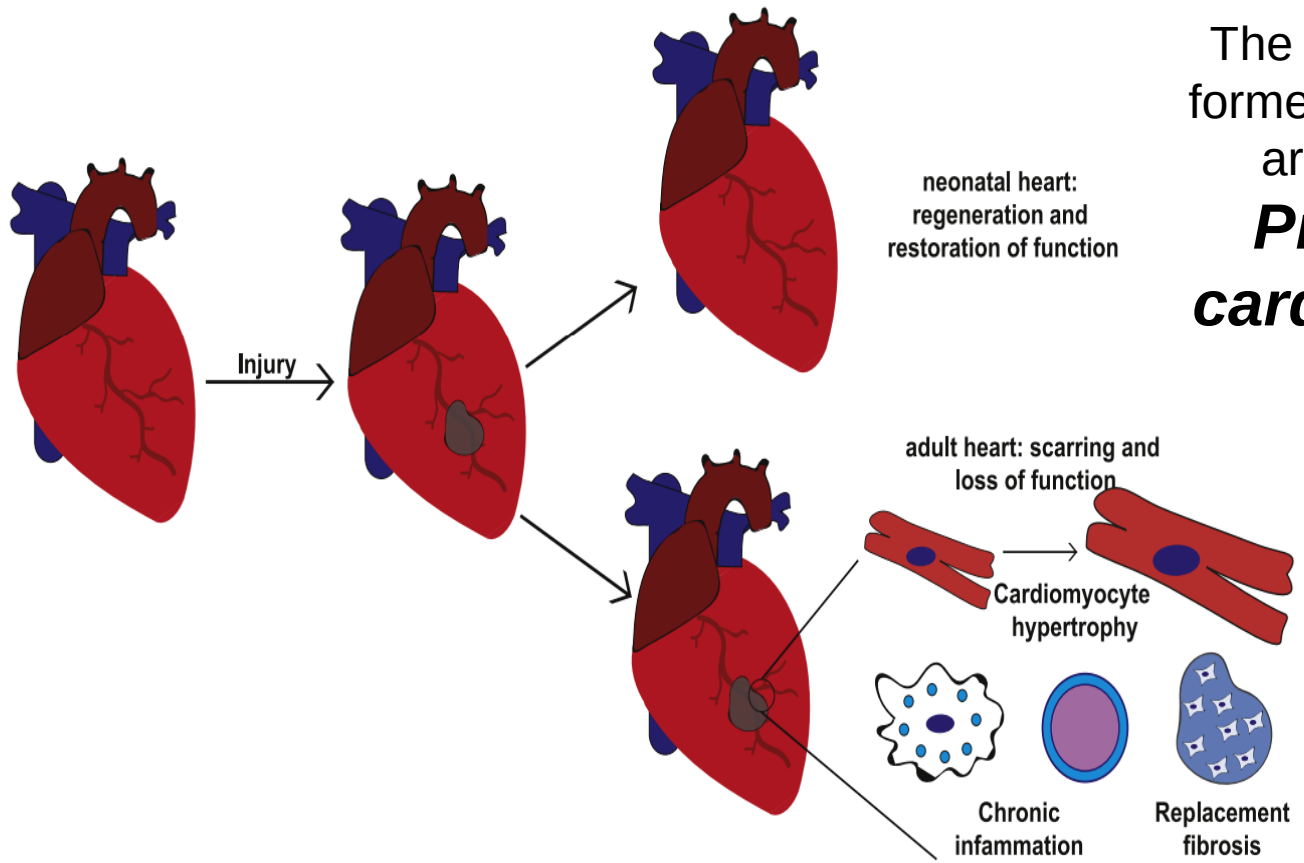
-to activate endogenous stem cells differentiation

-to activate progenitors such as cardiac stem cells (CSCs)

-to promote resident cardiomyocytes proliferation by inducing them to re-enter the cell cycle

Nature 2011 473, 326–335

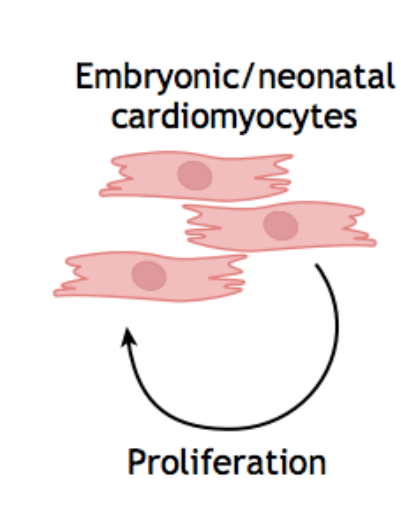
Neonatal heart regenerates after injury

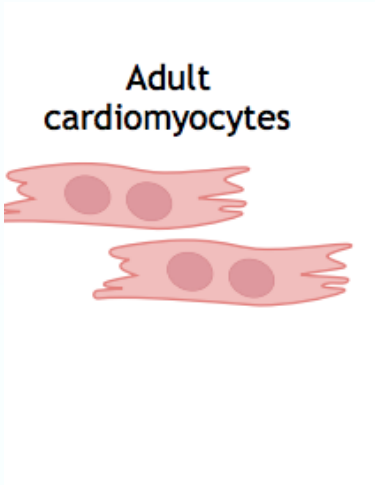


The majority of newly formed *cardiomyocytes* are derived from ***Pre-existing cardiomyocytes***

Lam and Sadek. Circulation 2018
Porrello et al. PNAS 2013 Porrello et al. Science 2011

Cardiac features : neonatal vs adult

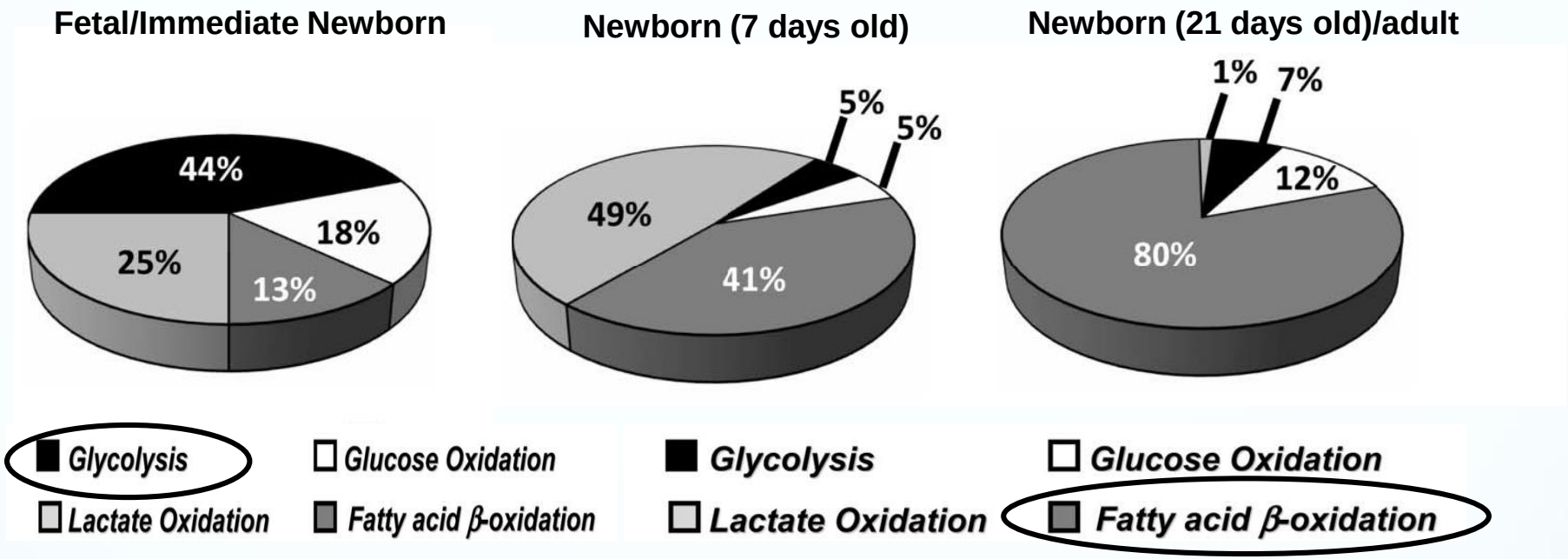




- cardiomyocytes are able to proliferate then gradually stop proliferating and exit the cell cycle (G0/G1 phase).
- cardiomyocytes are less differentiated.
- Cardiomyocytes can re-enter the cell cycle and proliferate.

- cardiomyocytes are **NOT** able to proliferate.
- cardiomyocytes are differentiated.
- Cardiomyocyte can re-enter the cell cycle but **not** undergo cell division (polyploidization and polynucleation).

Metabolism: neonatal vs adult



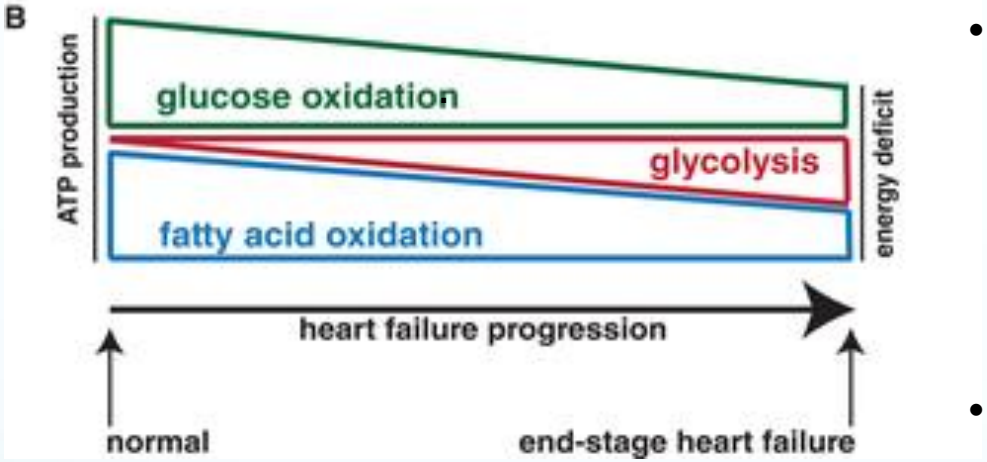
Anaerobic metabolism → Oxidative metabolism

Glucose → Fatty acids

J Cardiovasc PharmacolTM 2010;56:130–140

Metabolism in the failing heart

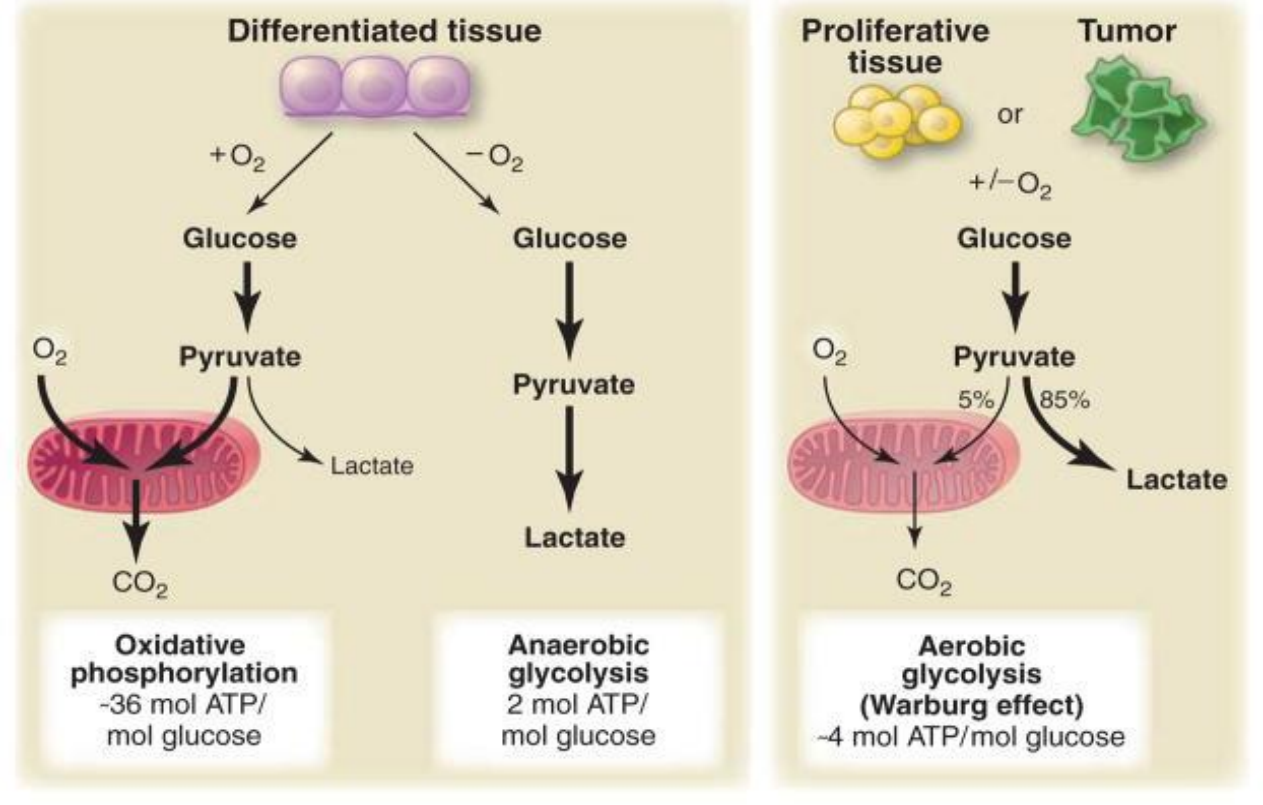
In the failing heart there is a substantial shift from fatty acid oxidation (FAO) towards increased glucose metabolism



- fatty acids can no longer be oxidized efficiently, leading to intracellular accumulation of fatty acids and their derivatives, provoking lipotoxicity
- the oxidation of glucose is more energy efficient than that of fatty acids
- the generation of glycolytic ATP in the cytoplasm is rapid and readily available for cell maintenance and protein synthesis.

Metabolism and cell cycle

In **proliferating cells** energy substrate metabolism is characterized by high rates of **glycolysis** even in the presence of adeguate oxigen.



The preferential use of aerobic glycolysis offers several advantages to higly proliferation cells concerning both bioenergetics and biosynthetic requirements

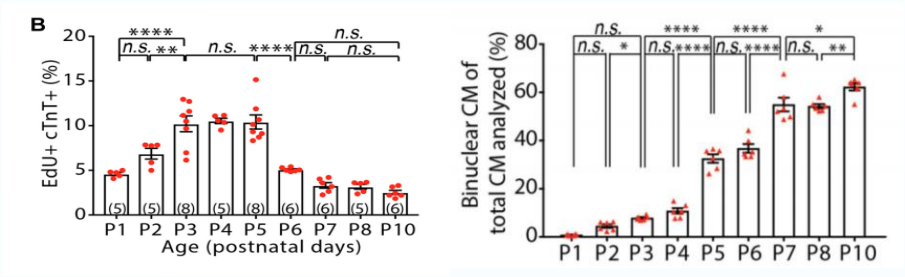
Vander Heiden MG Science 2009

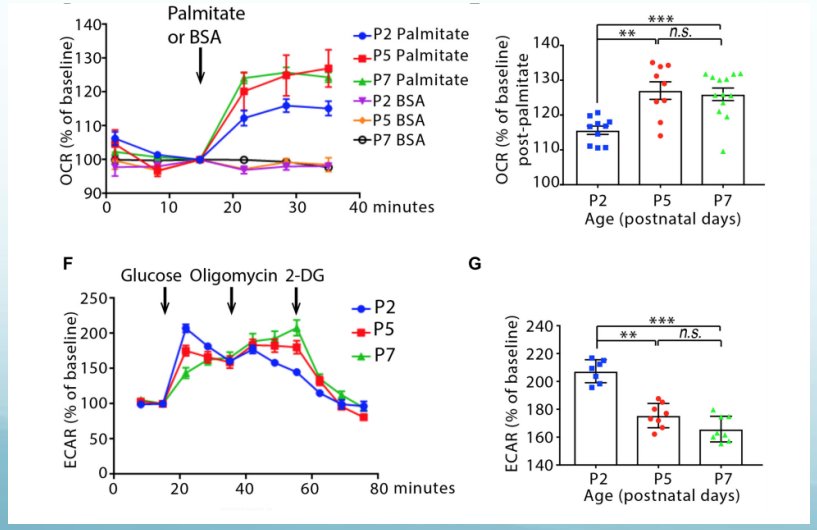
frontiers in Cell and Developmental Biology

ORIGINAL RESEARCH
published: 22 March 2019
doi: 10.3389/fcell.2019.00042

Fatty Acid Oxidation Promotes Cardiomyocyte Proliferation Rate but Does Not Change Cardiomyocyte Number in Infant Mice

Tongtong Cao[1,2†‡], Daniela Liccardo[1‡], Ryan LaCanna[1], Xiaoying Zhang[3], Rong Lu[2], Brian N. Finck[4], Tani Leigh[1], Xiongwen Chen[3], Konstantinos Drosatos[1] and Ying Tian[1]*

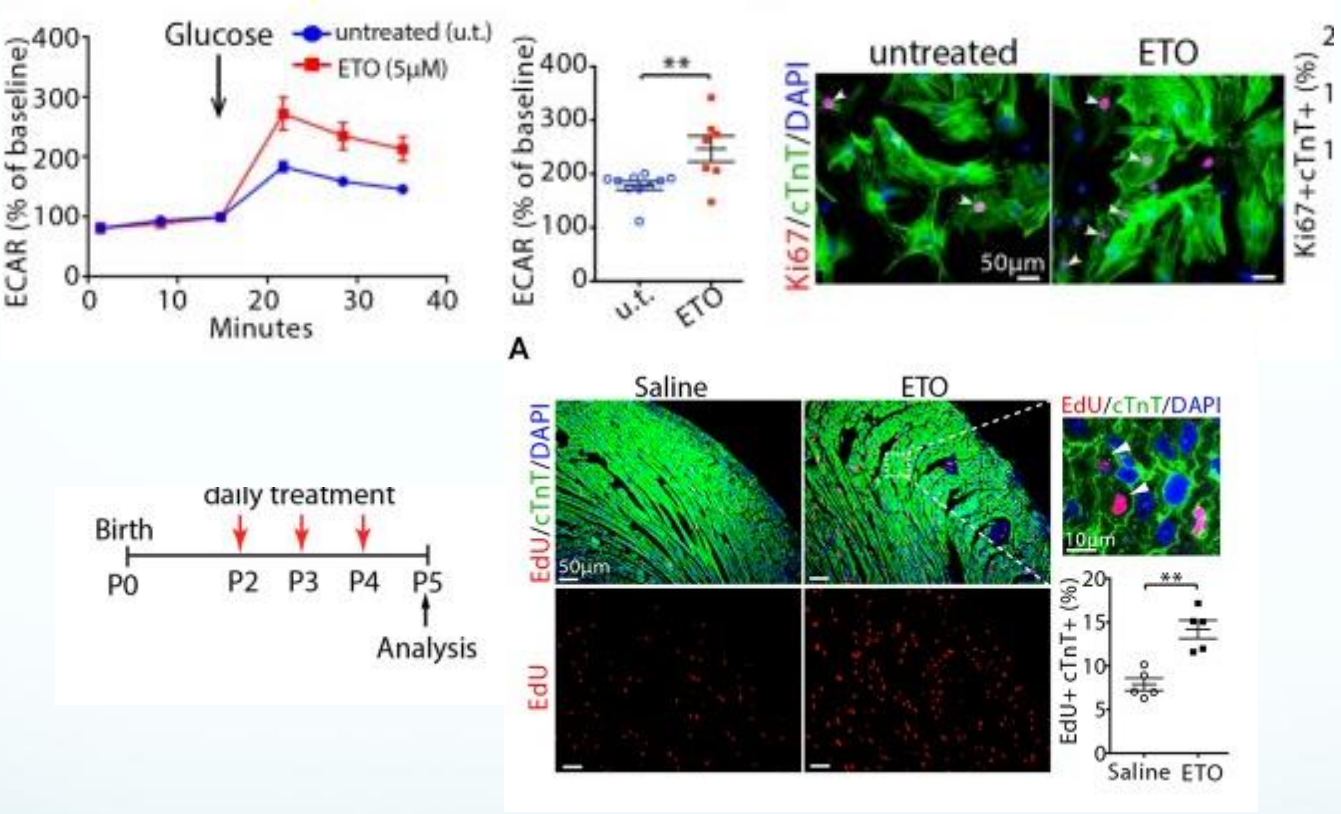




Cardiomyocytes proliferate in the postnatal life and exit the cell cycle between p3 and p5 becoming benucleated.

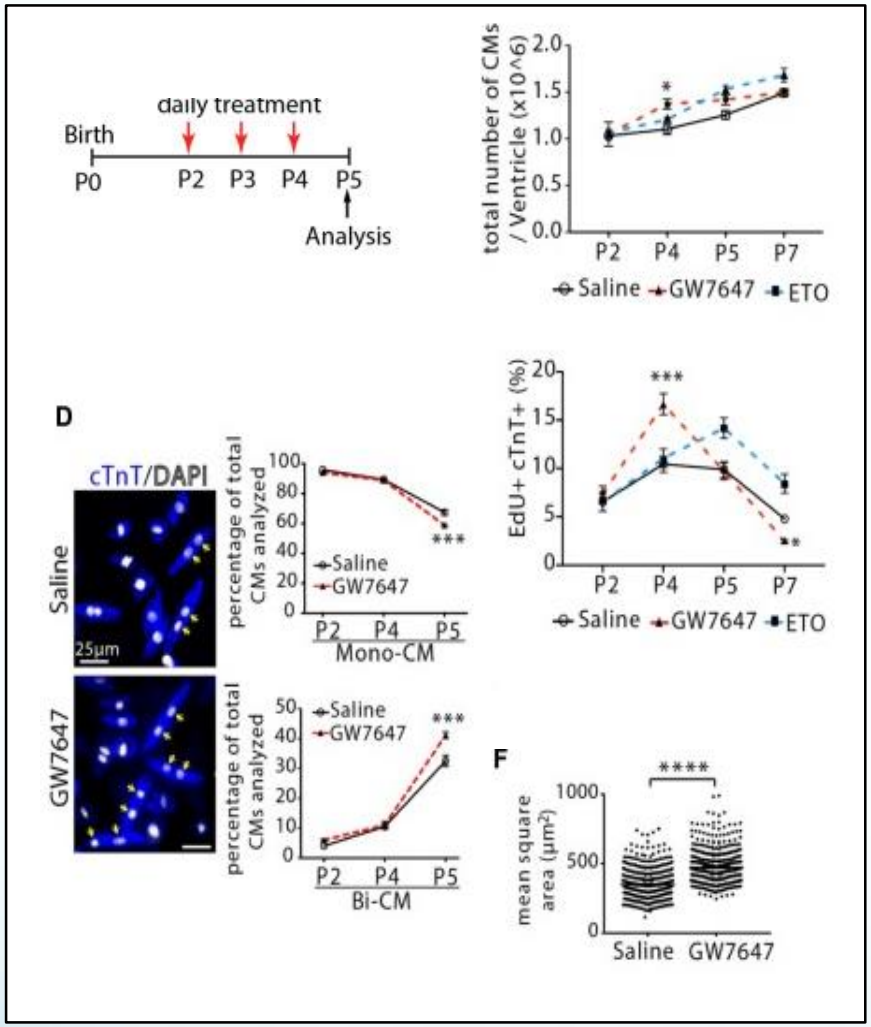
Cardiomyocytes exit cell cycle and Switch their metabolism to Fatty Acid β-Oxidation

Cao and Liccardo et al.Front Cell Dev Biol. 2019

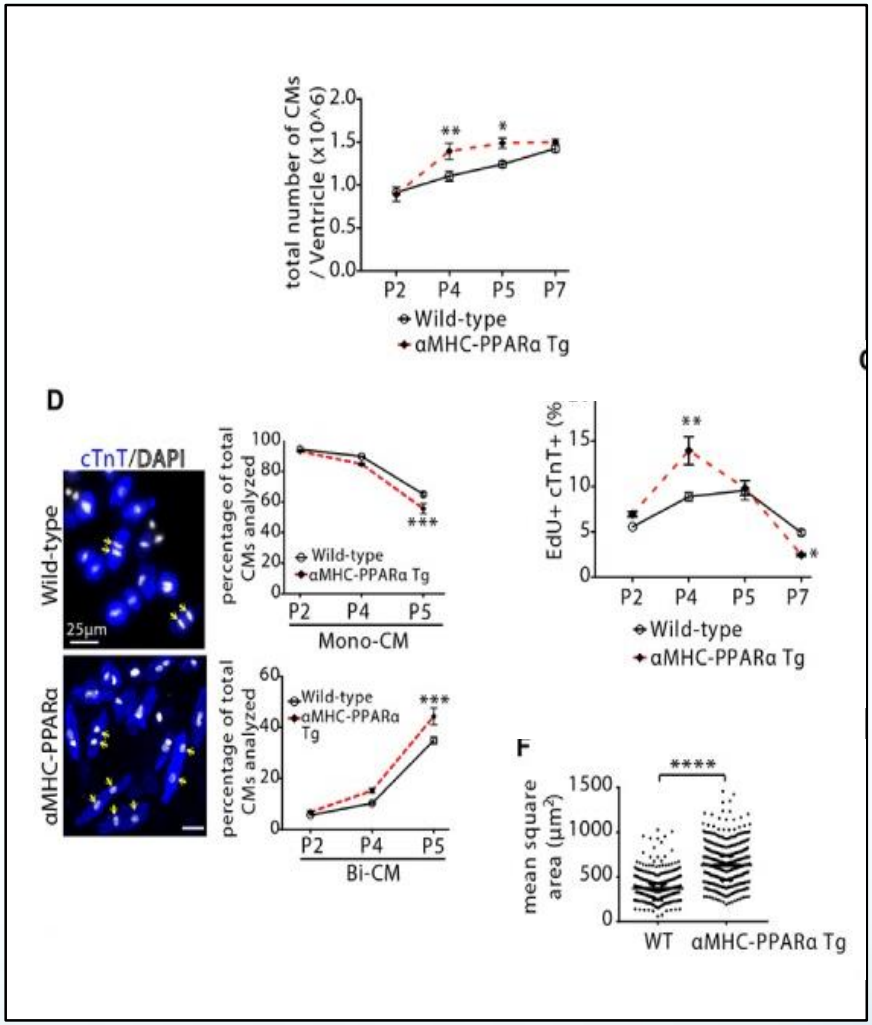


Inhibition of Cardiomyocyte Fatty Acid β-Oxidation Enhances Glycolysis and Maintains the Ability of Cardiomyocyte to Proliferate in Infant Mice

Cao and Liccardo et al. Front Cell Dev Biol. 2019



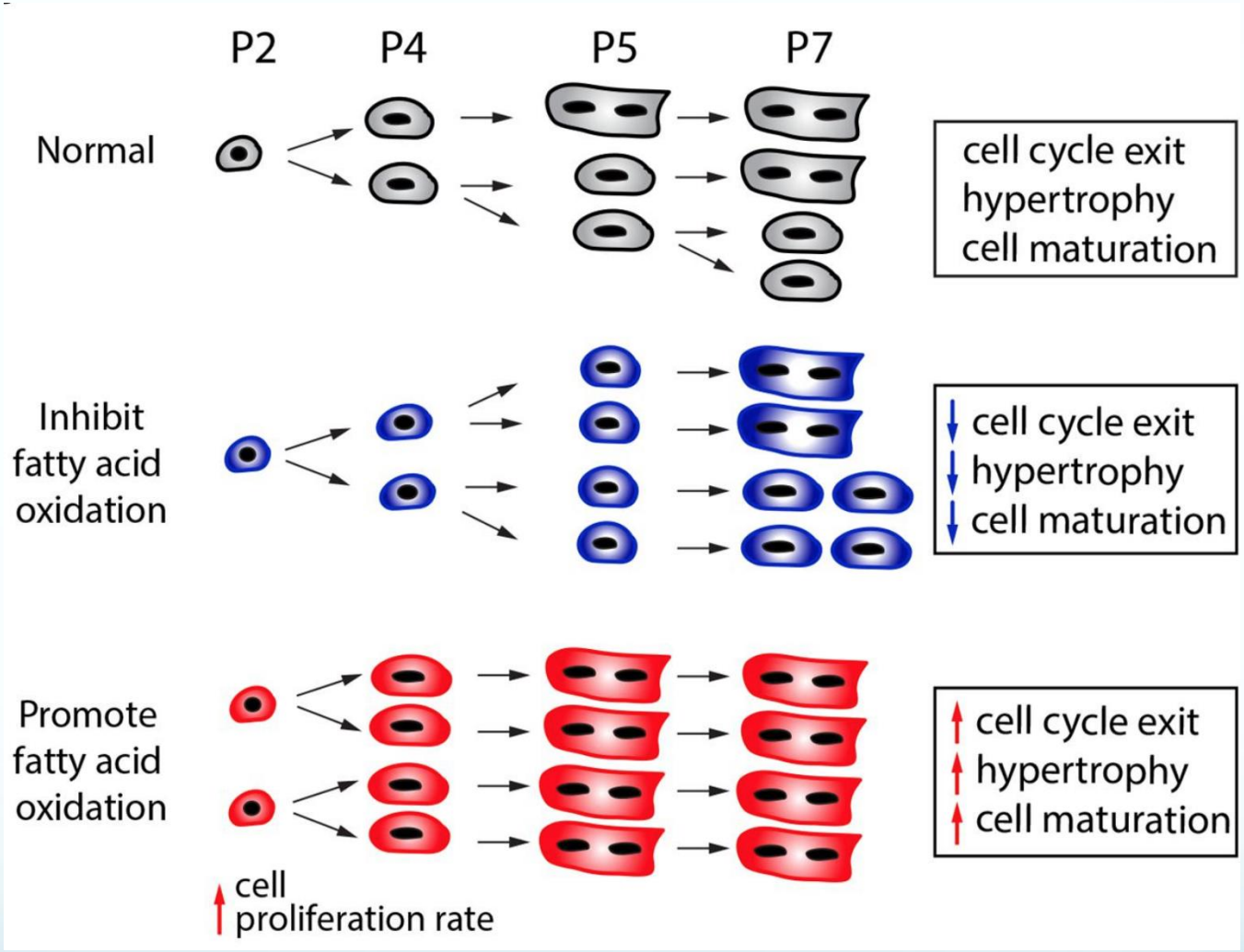
Stimulating PPARalpha



Overexpressing PPARalpha

Activation of Fatty Acid β-Oxidation Promotes Cell proliferation rate, Hypertrophic Growth and Binucleation

Cao and Liccardo et al.Front Cell Dev Biol. 2019

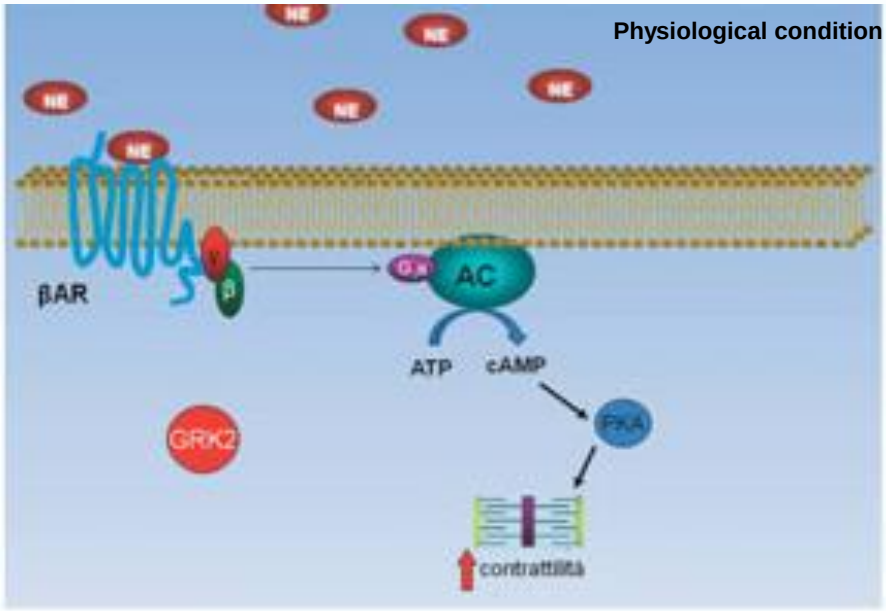


Oxidative metabolism plays an important role in enhancing cardiomyocyte proliferation rate

Cao and Liccardo et al.Front Cell Dev Biol. 2019

GRK2 in the heart

G protein-coupled receptor kinase (GRK2) is a serine/threonine kinase controlling the function of most of GPCRs present on cardiomyocytes and is involved in regulation of overall cardiovascular physiology.



Increased GRK2 is central to heart failure (HF) pathogenesis, via desensitization of β-adrenergic receptors and loss of contractile reserve.

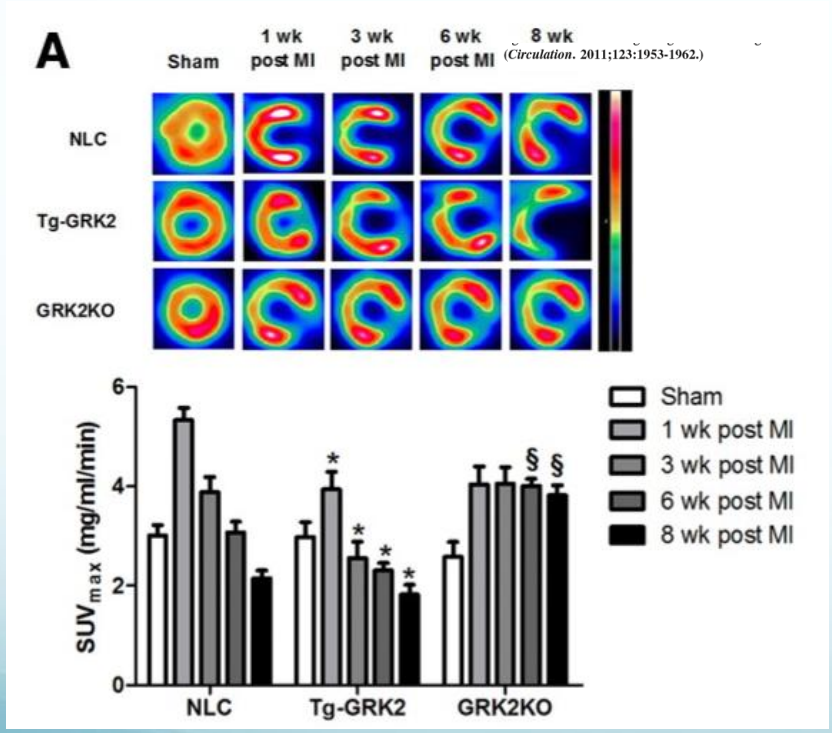
βARKct, reduces the capability of GRK2 to induce dysregulation and downregulation of β-adrenergic receptors increasing contractility.

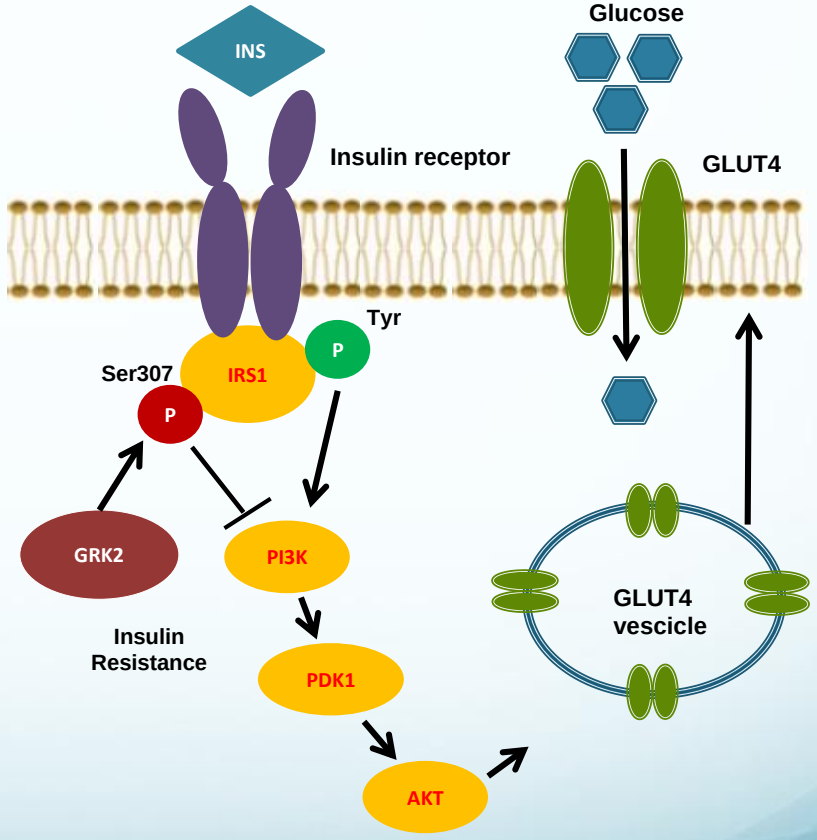
GRK2 impaires glucose uptake following myocardial infarction

Molecular Cardiology

G Protein–Coupled Receptor Kinase 2 Activity Impairs Cardiac Glucose Uptake and Promotes Insulin Resistance After Myocardial Ischemia

Michele Ciccarelli, MD, PhD; J. Kurt Chuprun, PhD; Giuseppe Rengo, MD, PhD; Erhe Gao, MD, PhD; Zhengyu Wei, PhD; Raymond J. Peroutka, BS; Jessica I. Gold, BS; Anna Gumpert, PhD; Mai Chen, MD, PhD; Nicholas J. Otis, BS; Gerald W. Dorn II, MD; Bruno Trimarco, MD; Guido Iaccarino, MD, PhD; Walter J. Koch, PhD





Grk2 overexpression reduces glucose uptake

J Mol Cell Cardiol. 2015 Dec;89(Pt B):360-4. doi: 10.1016/j.yjmcc.2015.10.002. Epub 2015 Oct 23.

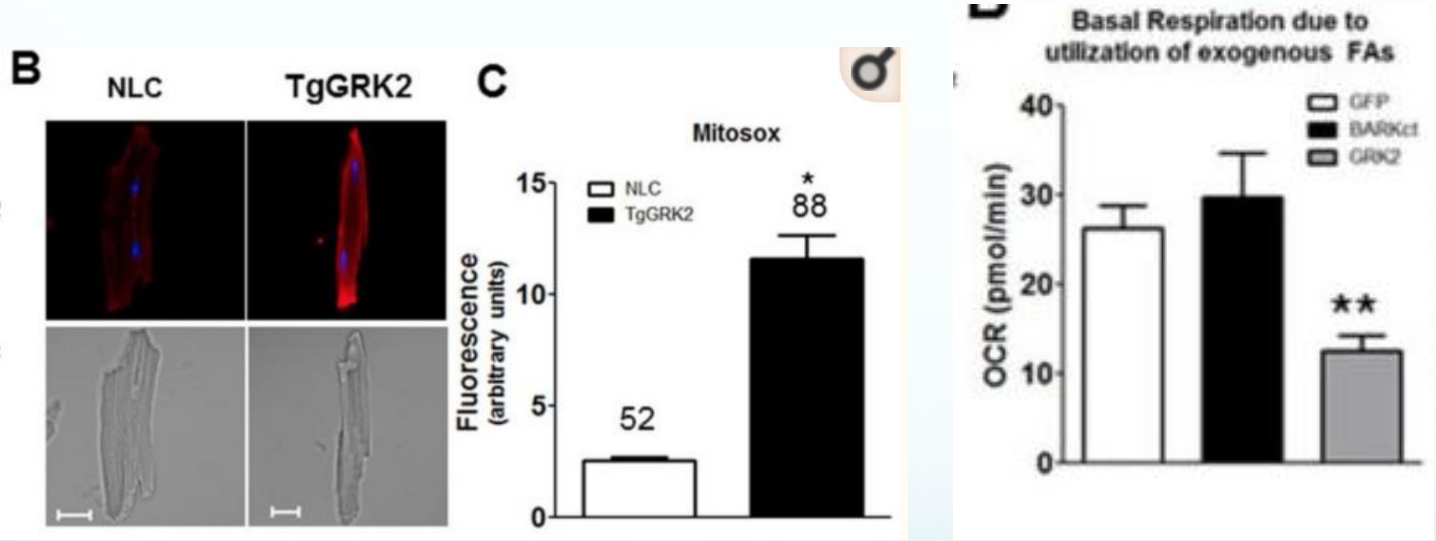
GRK2 compromises cardiomyocyte mitochondrial function by diminishing fatty acid-mediated oxygen consumption and increasing superoxide levels.

Sato PY[1], Chuprun JK[1], Ibetti J[1], Cannavo A[1], Drosatos K[1], Elrod JW[1], Koch WJ[2].

J Mol Cell Cardiol. 2018 Oct;123:108-117. doi: 10.1016/j.yjmcc.2018.08.025. Epub 2018 Aug 29.

G protein-coupled receptor kinase 2 contributes to impaired fatty acid metabolism in the failing heart.

Pfleger J[1], Gross P[2], Johnson J[2], Carter RL[1], Gao E[1], Tilley DG[1], Houser SR[2], Koch WJ[3].



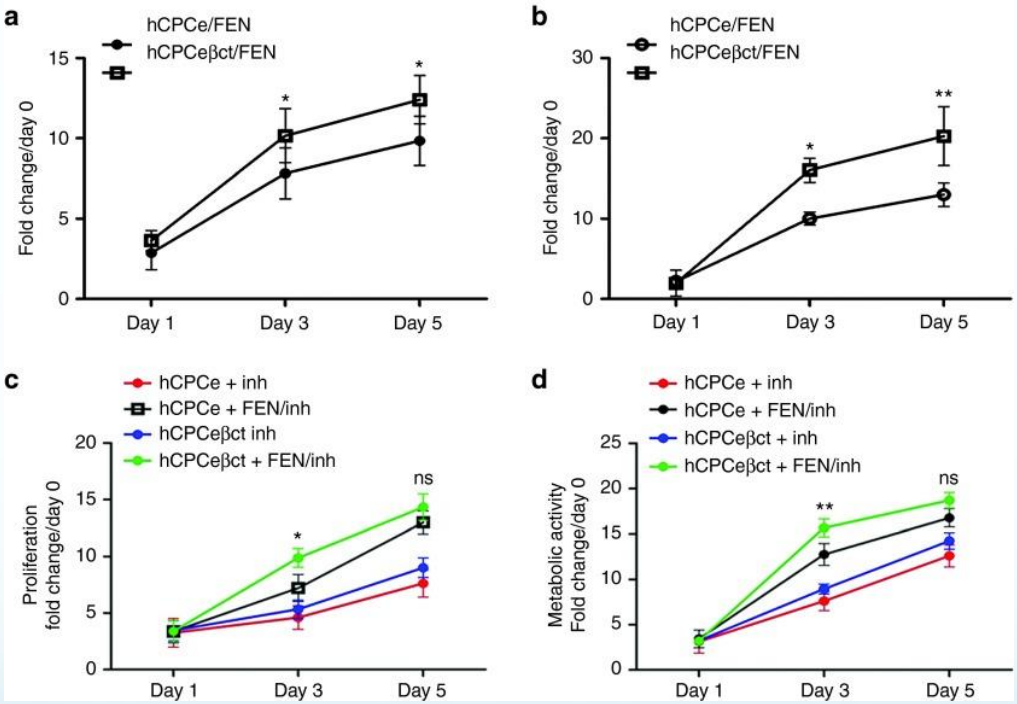
Overexpression of GRK2 in cardiomyocytes increases superoxide levels and reduces cell respiration and beta oxidation in cardiomyocytes and in HF

Mol Ther. 2014 Jan;22(1):178-85. doi: 10.1038/mt.2013.200. Epub 2013 Sep 3.

Cardiac progenitor cells engineered with βARKct have enhanced β-adrenergic tolerance.

Khan M[1], Mohsin S[1], Toko H[1], Alkatib M[1], Nguyen J[1], Truffa S[1], Gude N[1], Chuprun K[2], Tilley DG[2], Koch WJ[2], Sussman MA[1].

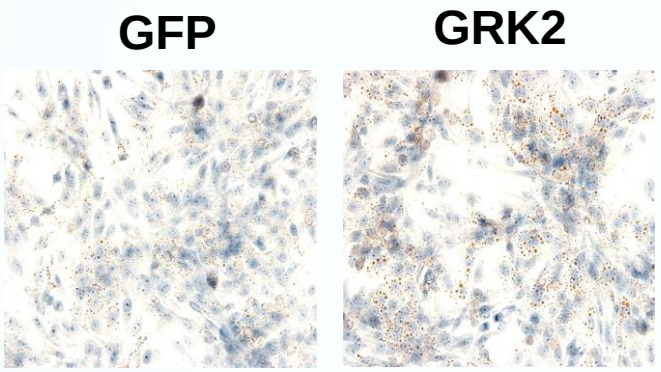
Author information

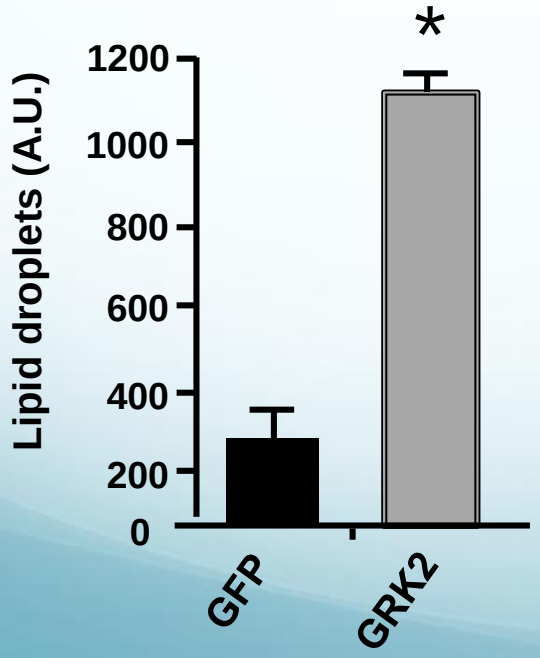


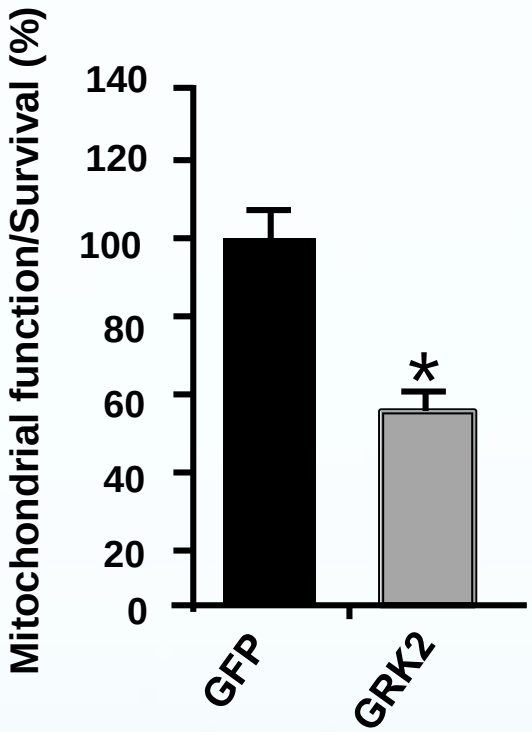
βARKct increases **proliferation** and **metabolic activity** in cardiac progenitor cells

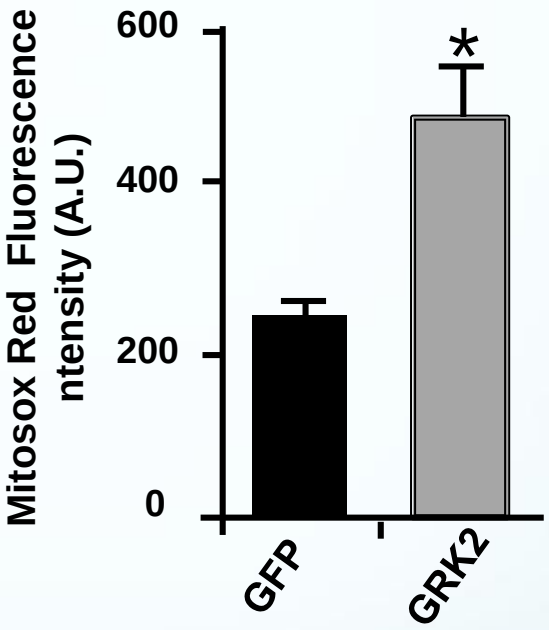
It is more than plausible to speculate that GRK2 impairing oxidative metabolism affects cardiac regeneration…..

GRK2 induces lipid accumulation and lipotoxicity





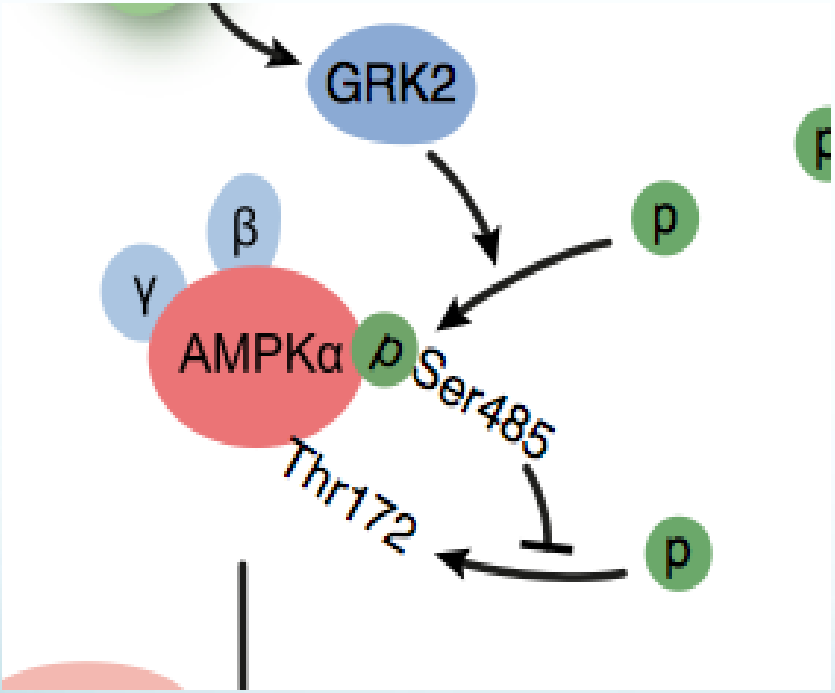




Cell Mol Life Sci. 2019 Nov;76(22):4423-4446. doi: 10.1007/s00018-019-03274-3. Epub 2019 Aug 20.

G protein-coupled receptor kinase 2 (GRK2) as a multifunctional signaling hub.

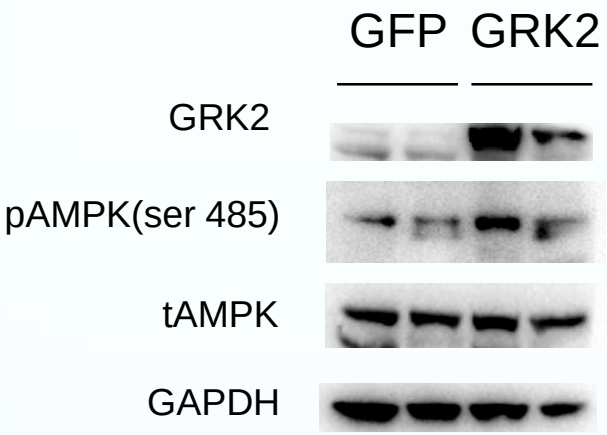
Penela P[1,2,3], Ribas C[1,2,3], Sánchez-Madrid F[2,3,4], Mayor F Jr[5,6,7].

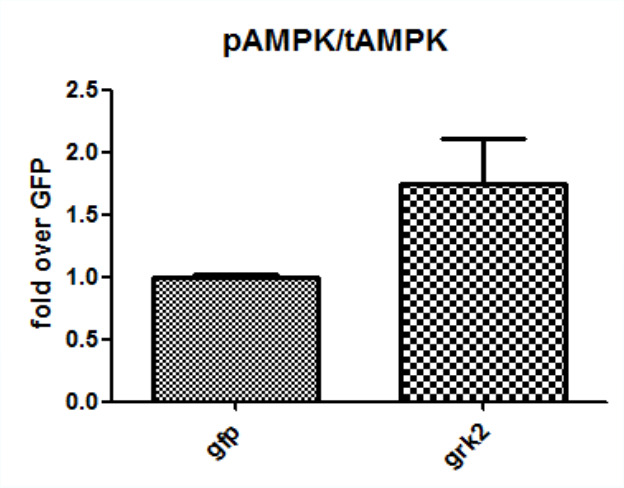


GRK2 binds to the **AMPK** α1 and α2 catalytic subunits and phosphorylates AMPK at Ser485, leading to the inhibition of AMPK Thr172 phosphorylation and its **inactivation**.

Diabetologia. 2018 May;61(5):1180-1192.

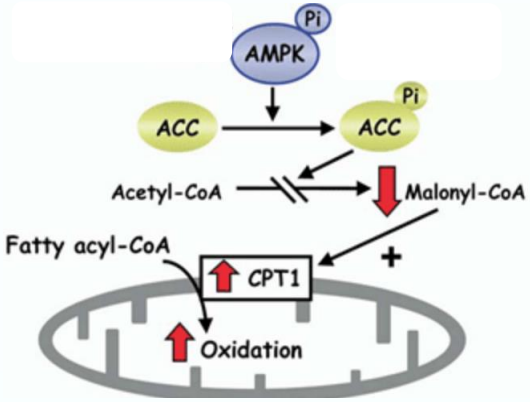
GRK2 reduces beta oxidation

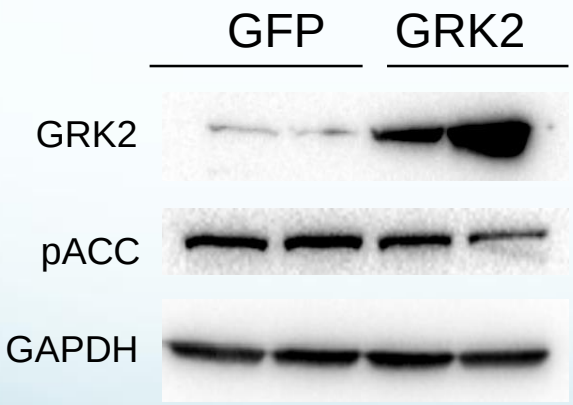


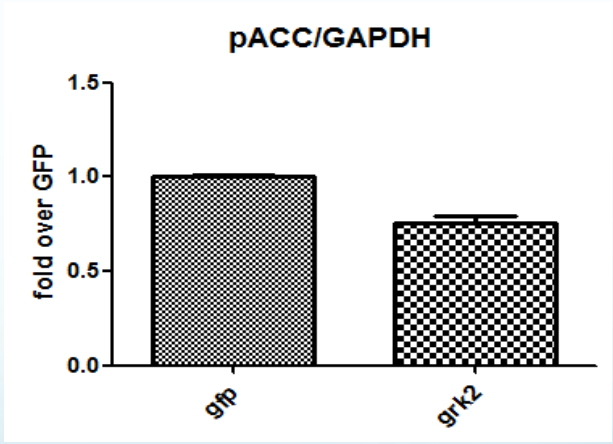


Grk2 reduces beta oxidation through AMPK inhibition

GRK2 reduces beta oxidation

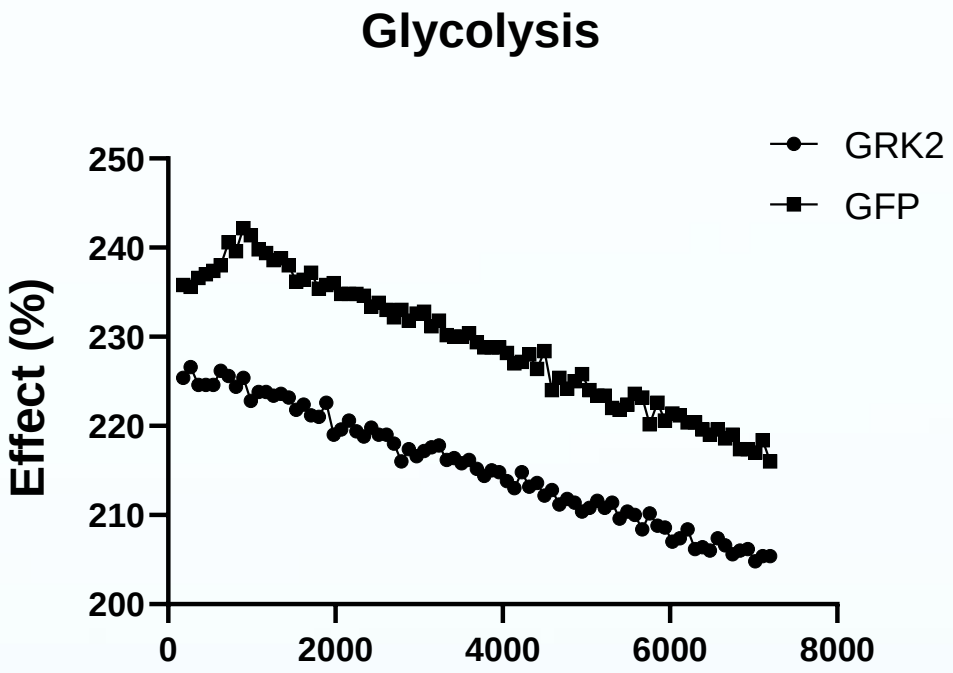




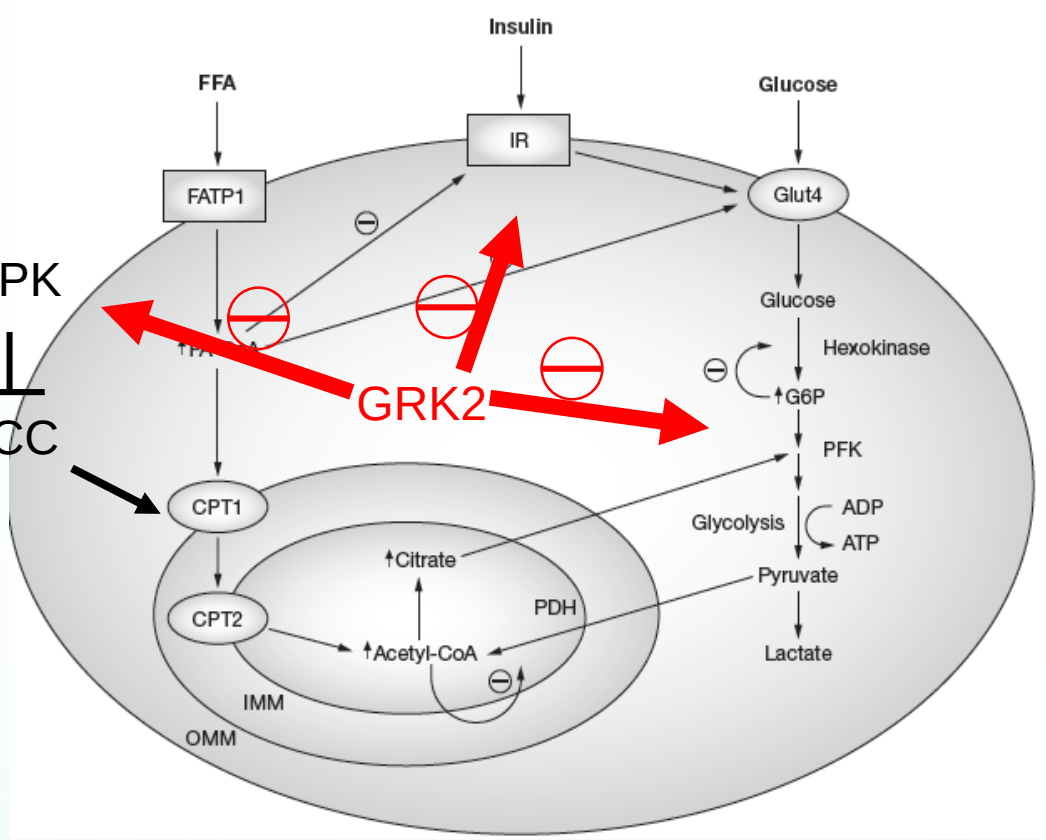


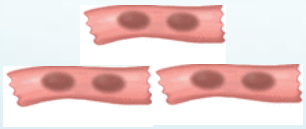
Grk2 reduces beta oxidation through AMPK/ACC inhibition

GRK2 affects glycolitic rate



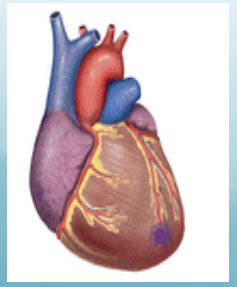
CONCLUSION





proliferation

Oxidative metabolism



Cardiac regeneration

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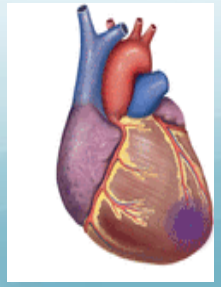

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Ying Tian, PhD

Thank you!