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INVITED REVIEW

The SAFE pathway for cardioprotection: is this a promising target?

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Abstract
The survivor activating factor enhancement (SAFE) pathway was discovered as an alternative intrinsic pro-survival signaling pathway to the reperfusion injury salvage kinase pathway for cardioprotection against ischemia–reperfusion injury. The delineation of this pathway, made of key components such as cytokines of the immune system and transcription factors, has brought major advancements in our understanding on how the heart is able to protect itself against ischemia–reperfusion injury. In this viewpoint, we describe the major steps leading to the discovery of the SAFE pathway in small animal models to date and we discuss its translation to large animals and humans.

Keywords Cardioprotection · Prosurvival signaling pathways · SAFE pathway · Immune system · Ischemia–reperfusion injury

Intrinsic cardiac signaling pathways to confer cardioprotection

Following the major discovery of the ischemic preconditioning (IPC) phenomenon (whereby small episodes of ischemia–reperfusion can confer cardioprotection against a sustained ischemic insult), it became evident that the heart has the ability to activate intrinsic cardioprotective signaling pathways to protect itself against different stress situations [42]. Over the past 30 years, intense research conducted with the aim to better understand the signaling process involved in ischemic conditioning has led to the discoveries of major key prosurvival molecules and has paved the way for potential novel therapeutic targets [16]. In the 90s, the role of adenosine, protein kinase C and the putative mitochondrial potassium–adenosine triphosphate dependent (mKATP) channel were amongst the key signaling components described in the cardioprotective signaling cascade of ischemic conditioning (see reviews [8, 9]). In 2002, Yellon's group described the reperfusion injury salvage kinase (RISK), highlighting the importance for the activation of the kinases protein kinase B (Akt) and extra regulated kinase (Erk) to limit ischemia–reperfusion injury with cardioprotective strategies [50]. At the same time, they also proposed that IPC protects the myocardium by inhibiting the mitochondrial permeability transition pore (mPTP) opening at reperfusion, thus reducing cardiomyocyte death by limiting uncoupling oxidative phosphorylation and swelling of the mitochondria [17]. In 2009, an important other step was made in the delineation of the cardioprotective signaling cascade with the discovery of the survivor activating factor enhancement pathway (SAFE) [34]. This path, triggered by the immune system, initiates the activation of a RISK-alternative pathway with a multitude of prosurvival signaling components, including the transcription factor signal transducer and activator of transcription 3 (STAT3) that targets the inhibition of the mPTP opening [4, 11, 31].

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The discovery of the SAFE pathway, from conception to birth: a 10 year fascinating journey

Officially born in 2009, the conception of the SAFE pathway goes back to 1999 with the discovery that tumor necrosis factor alpha (TNF), a key player of the immune system, could protect against ischemia–reperfusion injury when given as a preconditioning stimulus [36, 38]. At the time, this discovery was somewhat controversial as major clinical trials with anti-TNF in ischemic heart failure were initiated (RECOVER–RENAISSANCE–RECOVER) [1]. However, most clinical trials showed an adverse effect of the anti-TNF, a result that could be partly explained by our findings that TNF, in a dose and time dependent manner, can confer cardioprotection after binding to its receptor type 2 (TNFR2) [7, 32, 49, 51]. TNF is, in fact, an important signaling component contributing to the protection of both ischemic pre- and post-conditioning [32, 53]. Deciphering the signaling targets downstream of TNF for cardioprotection, protein kinase C, reactive oxygen species and mKATP channel were identified [37, 38]. To our surprise, the protective effect of TNF was not abolished in the presence of pharmacological inhibitors for Akt and Erk, therefore, suggesting that TNF confers cardioprotection via the activation of a RISK-alternative pathway [39]. Marber's group showed that protection with TNF is independent of p38 MAPK activation [58]. Also, the protection of TNF is abolished in the presence of an inhibitor of the Janus kinase (JAK)/STAT3 pathway or in cardiomyocytes of STAT3 knockout mice, therefore, suggesting that TNFR2 triggers the phosphorylation of JAK, which in turn, can trigger the phosphorylation of STAT3 on a tyrosine residue and its activation (after dimerization) [32, 39] (see review [45] for further details on STAT3 activation). This TNF/TNFR2/JAK/STAT3 pathway was named as the SAFE pathway and similar to the RISK path, it targets the inhibition of the mPTP opening to promote cardiomyocyte survival [4, 11, 18, 31, 34].

Although the activation of the SAFE pathway has been confirmed with multiple cardioprotective strategies [10, 24, 26, 29, 33, 48, 62], the understanding of the exact signaling cascade of this pathway is still in its infancy and many fundamental questions remain to be answered, including the following.

What are the trigger signaling components upstream of TNF?

Endogenous circulating components such as sphingosine-1 phosphate, melatonin, high density lipoproteins, and erythropoietin can activate the SAFE pathway [6, 33, 54, 59]. Although the toll like receptor 4 (TLR4) has been suggested to activate TNF as part of the SAFE path, the exact mechanism involved in TLR4 releasing TNF in the cardiomyocyte still remains to be elucidated [44] (see Fig. 1).

What is the cellular origin of TNF?

The presence of TNF has been identified in multiple cells ranging from inflammatory cells to cardiomyocytes and fibroblasts. To identify the cellular origin of TNF that activates survival signaling cascades against ischemia–reperfusion injury, we designed cardiomyocytes specific TNF knockout mice. In these mice, ischemic postconditioning failed to protect and activate STAT3, therefore, suggesting that TNF originating from the cardiomyocytes plays a major role in the activation of the SAFE pathway for cardioprotection [30].

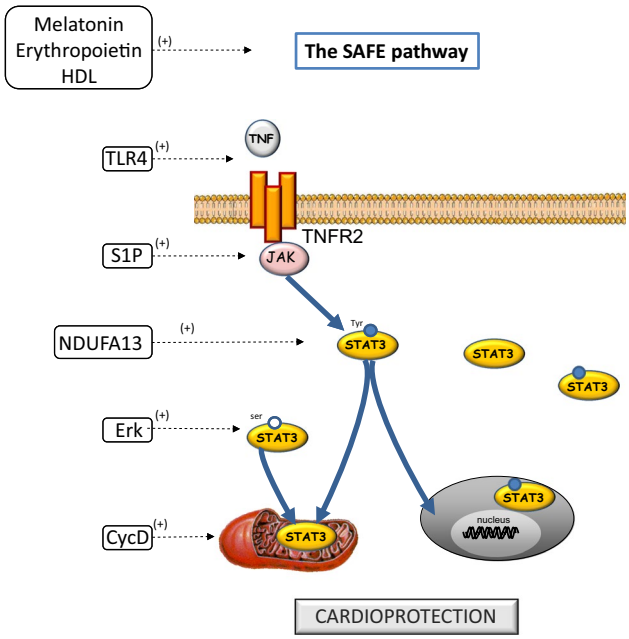

Fig. 1 Major components of the survivor activating factor enhancement (SAFE) pathway that promotes protection against ischemia–reperfusion injury. The activation of the SAFE pathway is triggered by the binding of TNF onto the TNF receptor 2 which, in turn, will activate the phosphorylation of JAK and STAT3. Melatonin, erythropoietin and HDL are endogenous circulatory molecules that can trigger the activation of the SAFE pathway. TLR4, S1P, NDUFA13, Erk and cyclophilin D will modulate the activation of the SAFE pathway. (+): stimulation. *CycD* cyclophilin D, *Erk* extra regulated kinase, *HDL* high density lipoprotein, *JAK* janus kinase, *NDUFA13* nicotinamide adenine dinucleotide dehydrogenase (ubiquinone) 1 alpha subcomplex 13, *Ser* serine, *S1P* sphingosine-1 phosphate, *STAT3* signal transducer and activator of transcription 3, *TLR4* toll like receptor 4, *TNF* tumor necrosis factor alpha, *TNFR2* TNF receptor 2, *Tyr* tyrosine

How can TNF activate STAT3 after binding to TNFR2?

Whereas the binding of JAK onto the interleukin-6 receptor is well described in the literature, no binding site for JAK has been identified on the TNFR2 until now. However, there is increasing evidence that activation of STAT3 by TNF is regulated by sphingosine kinase 1 and possibly sphingosine-1 phosphate [25, 46]. It is also suggested that the dimerization of STAT3 is controlled by nicotinamide adenine dinucleotide dehydrogenase (ubiquinone) 1 alpha subcomplex 13 (NDUFA13), a subunit of mitochondria complex I through the control of hydrogen peroxide formation by complex I [23].

What are the main downstream targets of STAT3?

Following stimulation by TNFR2, activated STAT3 interacts with Nuclear Factor kappa B signaling to upregulate mitochondrial fusion by activation of optic atrophy 1 (OPA1) expression [43]. It is now well established that phosphorylated STAT3 is present in both the nucleus and the mitochondria during ischemia–reperfusion [56, 57, 60]. The mitochondrial pool of STAT3 is dependent on phosphorylation of a serine residue and is stabilized by cyclophilin D, thus enabling STAT3 to regulate reactive oxygen species levels, the electron transport chain activity and the mPTP activity [4, 5, 40]. In pigs, phosphorylation of the tyrosine residue of STAT3 in the mitochondria mediates cardioprotection by postconditioning [19].

Does long-term stimulation of the SAFE pathway confer cardioprotection?

Although the transient activation of TNF and interleukin 6 at the onset of reperfusion is cardioprotective [38, 41], a chronic stimulation of the SAFE pathway is unlikely to benefit the heart [35]. In experimental ischemic heart failure, excess stimulation of TNF will contribute to inflammation, apoptosis and remodeling processes (via the TNF receptor 1) [15, 51]. Similarly, [19] inflammation and adverse cardiac remodeling is observed in mice with continuous activation of STAT3 [22]. In contrast, female cardiomyocyte STAT3 deficient mice develop postpartum cardiomyopathy which suggests that STAT3 may protect from postpartum oxidative stress [21].

SAFE pathway and cross talk with other cardioprotective components

Although many different intrinsic signaling molecules and mechanisms have been described in the heart, it is not quite clear yet whether these molecules interact with each other to confer cardioprotection. It is questionable as to whether the activation of both RISK and SAFE pathways is required to maximize the protection.

In fact, a cross-talk between the RISK and SAFE pathway has already been described. In STAT3 cardiomyocyte deficient mice or in the presence of a STAT3 inhibitor in wild-type mice, cardioprotective preconditioning strategies fail to protect and to activate components of the RISK pathway such as Akt and Erk [54, 55, 62]. Similarly, inhibition of the RISK pathway with Akt or Erk inhibitors results in the lack of protection of conditioning strategies and failure to activate STAT3 [54, 55]. In fact, Erk may also be a key player in the regulation of serine phosphorylation of mitochondrial STAT3 [14, 62].

Some cardioprotective strategies may require the activation of both RISK and SAFE pathways while other strategies may require only one of the two pathways for protection [24, 47, 48, 63]. However, caution needs to be taken when interpreting the published results as many studies have based their conclusion on western blot results only (absence of activation of Akt, STAT3 or Erk) performed at a very specific time point and without validating their results with the inhibition of the protein of interest. Considering that these proteins are activated at different time points during the reperfusion period, western blot data are clearly insufficient to draw any conclusion on the activation of the SAFE versus RISK pathway, unless kinetic studies with multiple time points are performed [27].

SAFE pathway and cardioprotection: from small to large animals to humans

To consider the SAFE pathway as a potential therapeutic target for novel cardioprotective strategies, it is critical to explore whether the activation of this pathway can be found in large animals and in humans with known cardioprotective strategies. Heusch's group has been able to demonstrate the translation from small animal models to a pig model whereby the activation of STAT3 with cardioprotective strategies such as ischemic pre- and post-conditioning as well as remote ischemic conditioning is required for the protection [13, 19, 52]. In humans, demonstrating the causal role of the SAFE pathway is challenging: activation of proteins can be identified but whether these proteins actually contribute to the protection remains to be validated. Nevertheless, Heusch's group elegantly measured the activation of various proteins in cardiac biopsies of patients subjected to remote ischemic preconditioning. To their surprise, activation of STAT5 but not STAT3 was increased in the presence of the conditioning stimulus, therefore, suggesting that STAT5 may play a critical role for cardioprotection in a human setting [20]. In children undergoing tetralogy of Fallot repair

surgery, remote ischemic preconditioning was associated with the activation of both STAT3 and STAT5 [61]. The increase in cytokine levels after remote ischemic conditioning could be observed for interleukin 1 alpha but not TNF [12].

Although the activation of the SAFE pathway offers a promising target for the development of novel therapeutic approaches to limit ischemia–reperfusion injury, the exact delineation of its signaling components in humans is critical as these might differ from small animals or even pigs. In addition, very little information is known about the effect of confounders and comorbidities on the activation of the SAFE pathway. Aging, obesity and propofol alter the activation of STATs [2, 3, 28] and a better understanding on the effect of such confounders on the SAFE path are required before cardioprotective strategies targeting the SAFE pathway can be considered in the clinical setting.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Balakumar P, Singh M (2006) Anti-tumour necrosis factor-alpha therapy in heart failure: future directions. Basic Clin Pharmacol Toxicol 99:391–397. https://doi.org/10.1111/j.1742-7843.2006.pto_508.x
2. Boengler K, Buechert A, Heinen Y, Roeskes C, Hilfiker-Kleiner D, Heusch G, Schulz R (2008) Cardioprotection by ischemic postconditioning is lost in aged and STAT3-deficient mice. Circ Res 102:131–135. https://doi.org/10.1161/CIRCRESAHA.107.164699
3. Boengler K, Hilfiker-Kleiner D, Drexler H, Heusch G, Schulz R (2008) The myocardial JAK/STAT pathway: from protection to failure. Pharmacol Ther 120:172–185. https://doi.org/10.1016/j.pharmthera.2008.08.002
4. Boengler K, Hilfiker-Kleiner D, Heusch G, Schulz R (2010) Inhibition of permeability transition pore opening by mitochondrial STAT3 and its role in myocardial ischemia/reperfusion. Basic Res Cardiol 105:771–785. https://doi.org/10.1007/s00395-010-0124-1
5. Boengler K, Ungefug E, Heusch G, Schulz R (2013) The STAT3 inhibitor static impairs cardiomyocyte mitochondrial function through increased reactive oxygen species formation. Curr Pharm Des 19:6890–6895. https://doi.org/10.2174/13816128193913112715940
6. Brulhart-Meynet MC, Braunersreuther V, Brinck J, Montecucco F, Prost JC, Thomas A, Galan K, Pelli G, Pedretti S, Vuilleumier N, Mach F, Lecour S, James RW, Frias MA (2015) Improving reconstituted HDL composition for efficient post-ischemic reduction of ischemia reperfusion injury. PLoS ONE 10:e0119664. https://doi.org/10.1371/journal.pone.0119664
7. Deuchar GA, Opie LH, Lecour S (2007) TNFalpha is required to confer protection in an in vivo model of classical ischaemic preconditioning. Life Sci 80:1686–1691. https://doi.org/10.1016/j.lfs.2007.01.040
8. Downey JM, Cohen MV (1997) Signal transduction in ischemic preconditioning. Adv Exp Med Biol 430:39–55. https://doi.org/10.1007/978-1-4615-5959-7_4
9. Downey JM, Davis AM, Cohen MV (2007) Signaling pathways in ischemic preconditioning. Heart Fail Rev 12:181–188. https://doi.org/10.1007/s10741-007-9025-2
10. Frias MA, Lecour S, James RW, Pedretti S (2012) High density lipoprotein/sphingosine-1-phosphate-induced cardioprotection: role of STAT3 as part of the SAFE pathway. JAKSTAT 1:92–100. https://doi.org/10.4161/jkst.19754
11. Frias MA, Pedretti S, Hacking D, Somers S, Lacerda L, Opie LH, James RW, Lecour S (2013) HDL protects against ischemia reperfusion injury by preserving mitochondrial integrity. Atherosclerosis 228:110–116. https://doi.org/10.1016/j.atherosclerosis.2013.02.003
12. Gedik N, Kottenberg E, Thielmann M, Frey UH, Jakob H, Peters J, Heusch G, Kleinbongard P (2017) Potential humoral mediators of remote ischemic preconditioning in patients undergoing surgical coronary revascularization. Sci Rep 7:12660. https://doi.org/10.1038/s41598-017-12833-2
13. Gent S, Skyschally A, Kleinbongard P, Heusch G (2017) Ischemic preconditioning in pigs: a causal role for signal transducer and activator of transcription 3. Am J Physiol Heart Circ Physiol 312:H478–H484. https://doi.org/10.1152/ajpheart.00749.2016
14. Gough DJ, Koetz L, Levy DE (2013) The MEK–ERK pathway is necessary for serine phosphorylation of mitochondrial STAT3 and Ras-mediated transformation. PLoS ONE 8:e83395. https://doi.org/10.1371/journal.pone.0083395
15. Hamid T, Gu Y, Ortines RV, Bhattacharya C, Wang G, Xuan YT, Prabhu SD (2009) Divergent tumor necrosis factor receptor-related remodeling responses in heart failure: role of nuclear factor-kappaB and inflammatory activation. Circulation 119:1386–1397. https://doi.org/10.1161/CIRCULATIONAHA.108.802918
16. Hausenloy DJ, Barrabes JA, Botker HE, Davidson SM, Di Lisa F, Downey J, Engstrom T, Ferdinandy P, Carbrera-Fuentes HA, Heusch G, Ibanez B, Iliodromitis EK, Inserte J, Jennings R, Kalia N, Kharbanda R, Lecour S, Marber M, Miura T, Ovize M, Perez-Pinzon MA, Piper HM, Przyklenk K, Schmidt MR, Redington A, Ruiz-Meana M, Vilahur G, Vinten-Johansen J, Yellon DM, Garcia-Dorado D (2016) Ischaemic conditioning and targeting reperfusion injury: a 30 year voyage of discovery. Basic Res Cardiol 111:70. https://doi.org/10.1007/s00395-016-0588-8
17. Hausenloy DJ, Duchen MR, Yellon DM (2003) Inhibiting mitochondrial permeability transition pore opening at reperfusion protects against ischaemia–reperfusion injury. Cardiovasc Res 60:617–625. https://doi.org/10.1016/j.cardiores.2003.09.025
18. Hausenloy DJ, Lecour S, Yellon DM (2011) Reperfusion injury salvage kinase and survivor activating factor enhancement prosurvival signaling pathways in ischemic postconditioning: two sides of the same coin. Antioxid Redox Signal 14:893–907. https://doi.org/10.1089/ars.2010.3360
19. Heusch G, Musiolik J, Gedik N, Skyschally A (2011) Mitochondrial STAT3 activation and cardioprotection by ischemic postconditioning in pigs with regional myocardial ischemia/reperfusion. Circ Res 109:1302–1308. https://doi.org/10.1161/CIRCRESAHA.111.255604
20. Heusch G, Musiolik J, Kottenberg E, Peters J, Jakob H, Thielmann M (2012) STAT5 activation and cardioprotection by remote ischemic preconditioning in humans: short communication. Circ Res 110:111–115. https://doi.org/10.1161/CIRCRESAHA.111.259556

21. Hilfiker-Kleiner D, Kaminski K, Podewski E, Bonda T, Schaefer A, Sliwa K, Forster O, Quint A, Landmesser U, Doerries C, Luchtefeld M, Poli V, Schneider MD, Balligand JL, Desjardins F, Ansari A, Struman I, Nguyen NQ, Zschemisch NH, Klein G, Heusch G, Schulz R, Hilfiker A, Drexler H (2007) A cathepsin D-cleaved 16 kDa form of prolactin mediates postpartum cardiomyopathy. Cell 128:589–600. https://doi.org/10.1016/j.cell.2006.12.036
22. Hilfiker-Kleiner D, Shukla P, Klein G, Schaefer A, Stapel B, Hoch M, Muller W, Scherr M, Theilmeier G, Ernst M, Hilfiker A, Drexler H (2010) Continuous glycoprotein-130-mediated signal transducer and activator of transcription-3 activation promotes inflammation, left ventricular rupture, and adverse outcome in subacute myocardial infarction. Circulation 122:145–155. https://doi.org/10.1161/CIRCULATIONAHA.109.933127
23. Hu H, Nan J, Sun Y, Zhu D, Xiao C, Wang Y, Zhu L, Wu Y, Zhao J, Wu R, Chen J, Yu H, Hu X, Zhu W, Wang J (2017) Electron leak from NDUFA13 within mitochondrial complex I attenuates ischemia–reperfusion injury via dimerized STAT3. Proc Natl Acad Sci USA. https://doi.org/10.1073/pnas.1704723114
24. Kalakech H, Hibert P, Prunier-Mirebeau D, Tamareille S, Letournel F, Macchi L, Pinet F, Furber A, Prunier F (2014) RISK and SAFE signaling pathway involvement in apolipoprotein A–I-induced cardioprotection. PLoS ONE 9:e107950. https://doi.org/10.1371/journal.pone.0107950
25. Karliner JS (2013) Sphingosine kinase and sphingosine 1-phosphate in the heart: a decade of progress. Biochim Biophys Acta 1831:203–212. https://doi.org/10.1016/j.bbalip.2012.06.006
26. Kelly RF, Lamont KT, Somers S, Hacking D, Lacerda L, Thomas P, Opie LH, Lecour S (2010) Ethanolamine is a novel STAT-3 dependent cardioprotective agent. Basic Res Cardiol 105:763–770. https://doi.org/10.1007/s00395-010-0125-0
27. Kleinbongard P, Skyschally A, Gent S, Pesch M, Heusch G (2018) STAT3 as a common signal of ischemic conditioning: a lesson on "rigor and reproducibility" in preclinical studies on cardioprotection. Basic Res Cardiol 113:3. https://doi.org/10.1007/s00395-017-0660-z
28. Kottenberg E, Musiolik J, Thielmann M, Jakob H, Peters J, Heusch G (2014) Interference of propofol with signal transducer and activator of transcription 5 activation and cardioprotection by remote ischemic preconditioning during coronary artery bypass grafting. J Thorac Cardiovasc Surg 147:376–382. https://doi.org/10.1016/j.jtcvs.2013.01.005
29. Kwan JC, Gao L, Macdonald PS, Hicks M (2015) Cardio-protective signalling by glyceryl trinitrate and cariporide in a model of donor heart preservation. Heart Lung Circ 24:306–318. https://doi.org/10.1016/j.hlc.2014.10.001
30. Lacerda L, Jacobs M, Opie L, Lecour S (2011) Ischaemic postconditioning confers protection via TNF: identifying the cellular origin of TNF. Eur Heart J 32:662. https://doi.org/10.1093/eurheartj/ehr324
31. Lacerda L, McCarthy J, Mungly SF, Lynn EG, Sack MN, Opie LH, Lecour S (2010) TNFalpha protects cardiac mitochondria independently of its cell surface receptors. Basic Res Cardiol 105:751–762. https://doi.org/10.1007/s00395-010-0113-4
32. Lacerda L, Somers S, Opie LH, Lecour S (2009) Ischaemic postconditioning protects against reperfusion injury via the SAFE pathway. Cardiovasc Res 84:201–208. https://doi.org/10.1093/cvr/cvp274
33. Lamont KT, Somers S, Lacerda L, Opie LH, Lecour S (2011) Is red wine a SAFE sip away from cardioprotection? Mechanisms involved in resveratrol- and melatonin-induced cardioprotection. J Pineal Res 50:374–380. https://doi.org/10.1111/j.1600-079X.2010.00853.x
34. Lecour S (2009) Activation of the protective survivor activating factor enhancement (SAFE) pathway against reperfusion injury: does it go beyond the RISK pathway? J Mol Cell Cardiol 47:32–40. https://doi.org/10.1016/j.yjmcc.2009.03.019
35. Lecour S, James RW (2011) When are pro-inflammatory cytokines SAFE in heart failure? Eur Heart J 32:680–685. https://doi.org/10.1093/eurheartj/ehq484
36. Lecour S, Minners J, Rochette L, Opie LH, Sack MN (1999) Tumor necrosis factor alpha confers cardiac preconditioning—possible role of mitochondrial KATP channel mediated event. Circulation 100:S768. https://doi.org/10.1161/01.CIR.100.18.s768
37. Lecour S, Rochette L, Opie L (2005) Free radicals trigger TNF alpha-induced cardioprotection. Cardiovasc Res 65:239–243. https://doi.org/10.1016/j.cardiores.2004.10.003
38. Lecour S, Smith RM, Woodward B, Opie LH, Rochette L, Sack MN (2002) Identification of a novel role for sphingolipid signaling in TNF alpha and ischemic preconditioning mediated cardioprotection. J Mol Cell Cardiol 34:509–518. https://doi.org/10.1006/jmcc.2002.1533
39. Lecour S, Suleman N, Deuchar GA, Somers S, Lacerda L, Huisamen B, Opie LH (2005) Pharmacological preconditioning with tumor necrosis factor-alpha activates signal transducer and activator of transcription-3 at reperfusion without involving classic prosurvival kinases (Akt and extracellular signal-regulated kinase). Circulation 112:3911–3918. https://doi.org/10.1161/CIRCULATIONAHA.105.581058
40. Meier JA, Hyun M, Cantwell M, Raza A, Mertens C, Raje V, Sisler J, Tracy E, Torres-Odio S, Gispert S, Shaw PE, Baumann H, Bandyopadhyay D, Takabe K, Larner AC (2017) Stress-induced dynamic regulation of mitochondrial STAT3 and its association with cyclophilin D reduce mitochondrial ROS production. Sci Signal. https://doi.org/10.1126/scisignal.aag2588
41. Muller J, Gorressen S, Grandoch M, Feldmann K, Kretschmer I, Lehr S, Ding Z, Schmitt JP, Schrader J, Garbers C, Heusch G, Kelm M, Scheller J, Fischer JW (2014) Interleukin-6-dependent phenotypic modulation of cardiac fibroblasts after acute myocardial infarction. Basic Res Cardiol 109:440. https://doi.org/10.1007/s00395-014-0440-y
42. Murry CE, Jennings RB, Reimer KA (1986) Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. Circulation 74:1124–1136. https://doi.org/10.1161/01.CIR.74.5.1124
43. Nan J, Hu H, Sun Y, Zhu L, Wang Y, Zhong Z, Zhao J, Zhang N, Wang Y, Wang Y, Ye J, Zhang L, Hu X, Zhu W, Wang J (2017) TNFR2 stimulation promotes mitochondrial fusion via Stat3- and NF-kB-dependent activation of OPA1 expression. Circ Res 121:392–410. https://doi.org/10.1161/CIRCRESAHA.117.311143
44. Nduhirabandi F, Lamont K, Albertyn Z, Opie LH, Lecour S (2016) Role of toll-like receptor 4 in melatonin-induced cardioprotection. J Pineal Res 60:39–47. https://doi.org/10.1111/jpi.12286
45. O'Sullivan KE, Breen EP, Gallagher HC, Buggy DJ, Hurley JP (2016) Understanding STAT3 signaling in cardiac ischemia. Basic Res Cardiol 111:27. https://doi.org/10.1007/s00395-016-0543-8
46. Pedretti S, Frias M, James R, Lecour S (2014) The cardioprotective effect of exogenous sphingosine-1-phosphate requires the activation of endogenous sphingosine-1-phosphate via the sphingosine kinase 1. Cardiovasc Res 103:S119. https://doi.org/10.1093/cvr/cvu098
47. Penna C, Perrelli MG, Tullio F, Angotti C, Camporeale A, Poli V, Pagliaro P (2013) Diazoxide postconditioning induces mitochondrial protein S-nitrosylation and a redox-sensitive mitochondrial phosphorylation/translocation of RISK elements: no role for SAFE. Basic Res Cardiol 108:371. https://doi.org/10.1007/s00395-013-0371-z

48. Penna C, Settanni F, Tullio F, Trovato L, Pagliaro P, Alloatti G, Ghigo E, Granata R (2013) GH-releasing hormone induces cardioprotection in isolated male rat heart via activation of RISK and SAFE pathways. Endocrinology 154:1624–1635. https://doi.org/10.1210/en.2012-2064
49. Sarzi-Puttini P, Atzeni F, Shoenfeld Y, Ferraccioli G (2005) TNF-alpha, rheumatoid arthritis, and heart failure: a rheumatological dilemma. Autoimmun Rev 4:153–161. https://doi.org/10.1016/j.autrev.2004.09.004
50. Schulman D, Latchman DS, Yellon DM (2002) Urocortin protects the heart from reperfusion injury via upregulation of p42/p44 MAPK signaling pathway. Am J Physiol Heart Circ Physiol 283:H1481–H1488. https://doi.org/10.1152/ajpheart.01089.2001
51. Schulz R, Heusch G (2009) Tumor necrosis factor-alpha and its receptors 1 and 2: Yin and Yang in myocardial infarction? Circulation 119:1355–1357. https://doi.org/10.1161/CIRCULATIONAHA.108.846105
52. Skyschally A, Gent S, Amanakis G, Schulte C, Kleinbongard P, Heusch G (2015) Across-species transfer of protection by remote ischemic preconditioning with species-specific myocardial signal transduction by reperfusion injury salvage kinase and survival activating factor enhancement pathways. Circ Res 117:279–288. https://doi.org/10.1161/CIRCRESAHA.117.306878
53. Smith RM, Lecour S, Sack MN (2002) Innate immunity and cardiac preconditioning: a putative intrinsic cardioprotective program. Cardiovasc Res 55:474–482. https://doi.org/10.1016/S0008-6363(02)00288-2
54. Somers SJ, Frias M, Lacerda L, Opie LH, Lecour S (2012) Interplay between SAFE and RISK pathways in sphingosine-1-phosphate-induced cardioprotection. Cardiovasc Drugs Ther 26:227–237. https://doi.org/10.1007/s10557-012-6376-2
55. Suleman N, Somers S, Smith R, Opie LH, Lecour SC (2008) Dual activation of STAT-3 and Akt is required during the trigger phase of ischaemic preconditioning. Cardiovasc Res 79:127–133. https://doi.org/10.1093/cvr/cvn067
56. Szczepanek K, Chen Q, Derecka M, Salloum FN, Zhang Q, Szelag M, Cichy J, Kukreja RC, Dulak J, Lesnefsky EJ, Larner AC (2011) Mitochondrial-targeted Signal transducer and activator of transcription 3 (STAT3) protects against ischemia-induced changes in the electron transport chain and the generation of reactive oxygen species. J Biol Chem 286:29610–29620. https://doi.org/10.1074/jbc.M111.226209
57. Szczepanek K, Xu A, Hu Y, Thompson J, He J, Larner AC, Salloum FN, Chen Q, Lesnefsky EJ (2015) Cardioprotective function of mitochondrial-targeted and transcriptionally inactive STAT3 against ischemia and reperfusion injury. Basic Res Cardiol 110:53. https://doi.org/10.1007/s00395-015-0509-2
58. Tanno M, Gorog DA, Bellahcene M, Cao X, Quinlan RA, Marber MS (2003) Tumor necrosis factor-induced protection of the murine heart is independent of p38-MAPK activation. J Mol Cell Cardiol 35:1523–1527. https://doi.org/10.1016/j.yjmcc.2003.09.019
59. Watson AJ, Gao L, Sun L, Tsun J, Jabbour A, Ru Qiu M, Jansz PC, Hicks M, Macdonald PS (2013) Enhanced preservation of the rat heart after prolonged hypothermic ischemia with erythropoietin-supplemented Celsior solution. J Heart Lung Transplant 32:633–640. https://doi.org/10.1016/j.healun.2013.03.014
60. Wegrzyn J, Potla R, Chwae YJ, Sepuri NB, Zhang Q, Koeck T, Derecka M, Szczepanek K, Szelag M, Gornicka A, Moh A, Moghaddas S, Chen Q, Bobbili S, Cichy J, Dulak J, Baker DP, Wolfman A, Stuehr D, Hassan MO, Fu XY, Avadhani N, Drake JI, Fawcett P, Lesnefsky EJ, Larner AC (2009) Function of mitochondrial Stat3 in cellular respiration. Science 323:793–797. https://doi.org/10.1126/science.1164551
61. Wu Q, Wang T, Chen S, Zhou Q, Li H, Hu N, Feng Y, Dong N, Yao S, Xia Z (2017) Cardiac protective effects of remote ischaemic preconditioning in children undergoing tetralogy of fallot repair surgery: a randomized controlled trial. Eur Heart J. https://doi.org/10.1093/eurheartj/ehx030
62. Yu L, Li B, Zhang M, Jin Z, Duan W, Zhao G, Yang Y, Liu Z, Chen W, Wang S, Yang J, Yi D, Liu J, Yu S (2016) Melatonin reduces PERK–eIF2alpha–ATF4-mediated endoplasmic reticulum stress during myocardial ischemia–reperfusion injury: role of RISK and SAFE pathways interaction. Apoptosis 21:809–824. https://doi.org/10.1007/s10495-016-1246-1
63. Zhao Y, Zheng ZN, Pi YN, Liang X, Jin SQ (2017) Cardioprotective effects of transfusion of late-phase preconditioned plasma may be induced by activating the reperfusion injury salvage kinase pathway but not the survivor activating factor enhancement pathway in rats. Oxid Med Cell Longev 2017:8526561. https://doi.org/10.1155/2017/8526561