

## Compensating for Cardiac Hypertrophy: A Crucial Role for A-Kinase Anchoring Protein-Lbc

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### Abstract

In response to mechanical load, cardiac hypertrophy (myocyte enlargement) is initially compensatory, but becomes a maladaptive process that leads to the development of heart failure. The high prevalence of pathological myocardial hypertrophy in cardiovascular disease coupled with a lack of effective treatment highlights a need for novel therapeutic strategies in this area.

Recently, a diverse family of scaffold proteins termed A-Kinase Anchoring Proteins have been identified and characterized, playing multiple important roles in the heart. In a recent study using a mouse model with a partial AKAP-Lbc (AKAP13) gene deletion, we demonstrate a crucial *in vivo* role for AKAP-Lbc-protein kinase D1 (PKD1) signaling in the development of compensatory hypertrophy in response to transverse aortic constriction (TAC)-induced pressure overload and neurohumoral stimulation by AT-II/PE treatment. Overall, our results show that AKAP-Lbc-PKD1 signaling is critical for transcriptional activation during the development of compensatory hypertrophy *in vivo*, under conditions of pathological hypertrophy. By defining and understanding regulation, downstream signaling and function of AKAP-Lbc-PKD1 signaling under pathological conditions, studies will determine whether AKAP-Lbc-PKD1 is a possible therapeutic target for treatment of cardiac dysfunction.

**Keywords:** Myocyte; Cardiac hypertrophy; Cardiac myocytes; AKAPs

### Background and Results Summary

In response to mechanical load, cardiac hypertrophy is initially compensatory, but becomes a maladaptive process that leads to the development of heart failure [1-3].

The high prevalence of pathological myocardial hypertrophy in cardiovascular disease coupled with a lack of effective treatment highlights a need for novel therapeutic strategies in this area. As such, modulation of myocardial growth without adversely affecting contractile function is increasingly recognized as a potential therapeutic approach in the prevention and treatment of heart failure [4].

Recently, a diverse family of scaffold proteins termed A-Kinase Anchoring Proteins have been identified and characterized in cardiac myocytes, playing multiple important roles in the heart, for example: yotiao [5], mAkap [6], synemin [7], AKAP15/18 [8], myospryn [9], AKAP79/150 [10], AKAP121 [11], troponin T [12] and AKAP-Lbc [13,14].

Much like the name suggests, a scaffold protein facilitates protein-protein interaction, often through specific protein-interaction domains determined by amino acid motifs contained within the scaffold protein and other cellular proteins [15]. Functionally, scaffold proteins act to assemble cellular signaling complexes and cascades of multiple enzymes [16].

AKAPs form multi-protein complexes, integrating cAMP-signaling with protein kinases, phosphatases and other effector proteins. Importantly, AKAPs function to modulate and target enzymes to distinct subcellular locations, thereby coordinating specific signaling events inside cells. Contextual regulation and location of enzyme activity impacts the control of cellular processes under normal and pathological conditions. Therefore, AKAP signaling complexes represent appealing therapeutic targets for disease treatment [17,18]. By defining and understanding regulation, downstream signaling and function of AKAP complexes (e.g. AKAP-Lbc, mAkap) under

pathological conditions, ongoing studies will determine whether AKAP-signaling complexes are viable therapeutic targets for treatment of cardiac dysfunction.

AKAP-Lbc-PKD1 signaling is critical in the induction of cardiac hypertrophy [14,15]. Therefore, in a recent study [19], we used a mouse model with a partial AKAP-Lbc (AKAP13) gene deletion coding for a region necessary for interaction with protein kinase D1 (PKD1, the major cardiac PKD isoform) [19]. Using this gene-trap mouse (which expresses a form of AKAP-Lbc that abolishes PKD1 binding: AKAP-Lbc-PKD), we studied two mouse models of pathological hypertrophy: i) Angiotensin (AT-II) and phenylephrine (PE) infusion and ii) Transverse aortic constriction (TAC)-induced pressure overload. Our results show that AKAP-Lbc-PKD mice exhibit an accelerated progression to cardiac dysfunction in response to AT-II/PE treatment and TAC. AKAP-Lbc-PKD mice display attenuated compensatory cardiac hypertrophy, increased collagen deposition and apoptosis, compared to wild-type (WT) control littermates. Mechanistically, reduced levels of PKD1 activation are observed in AKAP-Lbc-PKD mice compared to WT mice, resulting in diminished phosphorylation of histone deacetylase 5 (HDAC5) and decreased hypertrophic gene expression. This is consistent with a reduced compensatory hypertrophy phenotype leading to progression of heart failure in AKAP-Lbc-PKD mice, compared to wild-type littermates.

Overall, our data demonstrates a crucial *in vivo* role for AKAP-Lbc-

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PKD1 signaling in the development of compensatory hypertrophy to enhance cardiac performance in response to TAC-induced pressure overload and neurohumoral stimulation by AT-II/PE treatment. By interrogating genes differentially expressed between wild-type mice expressing the native form of AKAP-Lbc and AKAP-Lbc-PKD1 mice under pathological conditions, expression microarray analysis results show that AKAP-Lbc-PKD1 mice broadly fail to exhibit hypertrophy-responsive transcriptional activity found in WT mice. Identified differentially expressed genes in WT and AKAP-Lbc-PKD1 hearts are vital for the response to pressure-overload cardiac hypertrophy and include multiple myofibrillar and cell growth/differentiation genes.

In summary, our results show that AKAP-Lbc-PKD1 signaling is critical for transcriptional activation and repression during the development of compensatory hypertrophy *in vivo*, under conditions of pathological hypertrophy. If this compensatory pathway can be exploited, and we can understand the signaling transduction involved in transition to a decompensatory phase leading to cardiac dysfunction, then it may be possible to mitigate the development of heart failure, thereby improving patient mortality.

#### References

1. Chien KR, Olson EN (2002) Converging pathways and principles in heart development and disease: CV@CSH. *Cell* 110: 153-162.
2. Carnegie GK, Burmeister BT (2011) A-kinase anchoring proteins that regulate cardiac remodeling. *J Cardiovasc Pharmacol* 58: 451-458.
3. Heineke J, Molkentin JD (2006) Regulation of cardiac hypertrophy by intracellular signalling pathways. *Nat Rev Mol Cell Biol* 7: 589-600.
4. Mudd JO, Kass DA (2008) Tackling heart failure in the twenty-first century. *Nature* 451: 919-928.
5. Bauman AL, Michel JJ, Henson E, Dodge-Kafka KL, Kapiloff MS (2007) The mAKAP signalosome and cardiac myocyte hypertrophy. *IUBMB Life* 59: 163-169.
6. Russell MA, Lund LM, Haber R, McKeegan K, Cianciola N, et al. (2006) The intermediate filament protein, synemin, is an AKAP in the heart. *Arch Biochem Biophys* 456: 204-215.
7. Gray PC, Tibbs VC, Catterall WA, Murphy BJ (1997) Identification of a 15-kDa cAMP-dependent protein kinase-anchoring protein associated with skeletal muscle L-type calcium channels. *J Biol Chem* 272: 6297-6302.
8. Reynolds JG, McCalmon SA, Tomczyk T, Naya FJ (2007) Identification and mapping of protein kinase a binding sites in the costameric protein myospryn. *Biochim Biophys Acta* 1773: 891-902.
9. Nichols CB, Rossow CF, Navedo MF, Westenbroek RE, Catterall WA, et al. (2010) Sympathetic stimulation of adult cardiomyocytes requires association of AKAP5 with a subpopulation of L-type calcium channels. *Circ Res* 107: 747-756.
10. Abrenica B, AlShaaban M, Czubyrt MP (2009) The A-kinase anchor protein AKAP121 is a negative regulator of cardiomyocyte hypertrophy. *J Mol Cell Cardiol* 46: 674-681.
11. Sumandea CA, Garcia-Cazarin ML, Bozio CH, Sievert GA, Balke CW, et al. (2011) Cardiac troponin T, a sarcomeric AKAP, tethers protein kinase A at the myofilaments. *J Biol Chem* 286: 530-541.
12. Carnegie GK, Soughayer J, Smith FD, Pedroja BS, Zhang F, et al. (2008) AKAP-Lbc mobilizes a cardiac hypertrophy signaling pathway. *Mol Cell* 32: 169-179.
13. Appert-Collin A, Cotecchia S, Nenniger-Tosato M, Pedrazzini T, Diviani D (2007) The a-kinase anchoring protein(akap)-lbc-signaling complex mediates alpha1adrenergic receptor-induced cardiomyocyte hypertrophy. *Proc Natl Acad Sci U S A* 104: 10140-10145
14. [http://pawsonlab.mshri.on.ca/index.php?option=com\\_content&task=view&id=30&Itemid=63](http://pawsonlab.mshri.on.ca/index.php?option=com_content&task=view&id=30&Itemid=63)
15. Diviani D, Dodge-Kafka KL, Li J, Kapiloff MS (2011) A-kinase anchoring proteins: scaffolding proteins in the heart. *Am J Physiol Heart Circ Physiol* 301: H1742-1753.
16. Negro A, Dodge-Kafka K, Kapiloff MS (2008) Signalosomes as Therapeutic Targets. *Prog Pediatr Cardiol* 25: 51-56.
17. Tröger J, Moutty MC, Skroblin P, Klusmann E (2012) A-kinase anchoring proteins as potential drug targets. *Br J Pharmacol* 166: 420-433.
18. Taglieri DM, Johnson KR, Burmeister BT, Monasky MM, Spindler MJ, et al. (2014) The C-terminus of the long AKAP13 isoform (AKAP-Lbc) is critical for development of compensatory cardiac hypertrophy. *J Mol Cell Cardiol* 66: 27-40.
19. Spindler MJ, Burmeister BT, Huang Y, Hsiao EC, Salomonis N (2013) AKAP13 Rho-GEF and PKD-Binding Domain Deficient Mice Develop Normally but Have an Abnormal Response to  $\beta$ -Adrenergic-Induced Cardiac Hypertrophy. *PLoS ONE* 8.