JDP2 in Cardiac Disease

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Heart failure (HF) and atrial fibrillation (AF) are two major life-threatening diseases worldwide. Causes and mechanisms are incompletely understood, yet current therapies are unable to stop disease progression. In our study, we focus on the contribution of the transcriptional modulator, Jun dimerization protein 2 (JDP2), and on HF and AF development. In recent years, JDP2 has been identified as a potential prognostic marker for HF development after myocardial infarction. This close correlation to the disease development suggests that JDP2 may be involved in initiation and progression of HF as well as in cardiac dysfunction.

heart failure atrial fibrillation transcription factor remodeling

1. Transcriptional Control by JDP2

JDP2 belongs to the leucine zipper superfamily of transcription factors that predominantly binds to the promoter elements cAMP response element (CRE) or 12-O-tetradecanoylphorbol-13-acetate (TPA) response element (TRE) [1][2]. It was originally described as a transcriptional repressor of activator protein 1 (AP-1). JDP2 displaces the typical binding partner from the AP-1 dimer, thereby producing a transcriptionally inactive complex. Meanwhile, it became clear that JDP2 not only represses transcription via the AP-1 blockade, but also via binding to core histones and nucleosomes in a sequence specific manner. In this situation, JDP2 provokes chromatin remodeling, since it prevents histone modifying and transcription promoting enzymes, such as histone acetyltransferases (HAT) or methylases, from accessing the nucleosome [3][4]. In addition, JDP2 can recruit histone deacetylases into the complex as a further regulating step in transcriptional Inhibition [5][6][7]. Besides these pleiotropic effects on transcriptional repression, JDP2 can also activate transcription. It acts as a coactivator of the progesterone receptor[8][9][10][11]. By binding to anti-oxidant responsive element (ARE) sites, in association with the Nrf2/MafK complex, JDP2 promotes the transcription of antioxidant genes[12][13]. Thus, overall it can be said, that JDP2 primarily acts as a sequence specific inhibitor of transcription, but in some instances it may also promote transcription.

2. Correlation between JDP2 Expression and Heart Failure

The first report about the association of increased JDP2 expression after myocardial infarction (MI) with HF progression was published by Maciejak and coworkers in 2015[14]. They collected peripheral blood samples from patients with acute myocardial infarction (AMI) at admission and at three consecutive dates following admission, with the latest 6 months after AMI. Gene profiling in peripheral blood mononuclear cells (PBMCs) of these patients revealed differential gene expression at admission in patient groups that developed HF within 6 months after AMI

compared to the patient group who did not. JDP2 was among these differentially expressed genes with an upregulation at admission and up to 6 days after AMI. Thus, JDP2 expression in AMI patients indicates a more severe initial damage to the heart, which then culminates in HF at later time points. In another study, Qui and Liu[15] analyzed two independent datasets from gene expression studies of peripheral blood cells from MI patients, and identified 477 conserved genes that were differentially expressed in both datasets, and JDP2 was one of them. The latest study revealing JDP2 as a prognostic marker for HF development was just recently published[16]. Within 1007 differentially expressed mRNAs, JDP2 belonged to the top 20 differentially expressed mRNAs.

3. Influence of JDP2 on Ventricular Remodeling and Function

Overexpression of JDP2 for one week in adult mice provoked ventricular dysfunction, since cardiac output, fractional shortening, and ejection fraction declined. This ventricular dysfunction aggravated during prolongation of JDP2 overexpression up to five weeks[17]. Contractile dysfunction was observed also on a cellular level. Isolation of ventricular cardiomyocytes from these mice revealed reduced cell shortening and contraction velocity under electrical stimulation after one week of JDP2 overexpression. After prolonged JDP2 overexpression, the contractile capacity declined further, and after lifelong JDP2 overexpression, positive inotropic effects by beta-adrenergic stimulation were abolished[18].

Surprisingly, JDP2 KO did not protect the heart against pressure overload induced damage following transverse aortic constriction (TAC). Instead, the JDP2 KO mice performed worse than wild type[19]. Thus, in response to pressure overload the absence of JDP2 caused stronger ventricular impairments compared to WT mice. However, hypertrophic enlargement of the heart was already detectable in JDP2 KO mice without any additional provocation, indicating that basal JDP2 expression is responsible for the control of cardiac size and function in the healthy heart. However, when the heart is exposed to sustained stress, i.e., under pressure overload or JDP2 overexpression, contractile impairment of cardiomyocytes assumes the prevailing role and HF progresses.

4. JDP2 Promotes Atrial Remodeling and Arrhythmias

Much clearer, and without any doubt, is the influence of JDP2 on the induction of atrial arrhythmias, such as conduction defects or AF. Already the first description of transgenic JDP2 mice with a continuous cardio-specific JDP2 overexpression from birth up to 4 weeks of age characterized JDP2 as a major mediator of massive bi-atrial dilatation[20]. ECG recordings on anesthetized animals revealed conduction abnormalities and occurrence of AF. The observed connexin 40 downregulation under JDP2 overexpression may contribute to prolongation of atrial conduction times, since the electrical coupling is reduced in connexin KO mice[21]. Interestingly, arrhythmias and atrial dilatation were almost fully reversible upon cessation of JDP2 overexpression[20]. The absence of ventricular impairments at that time point under JDP2 expression in juvenile mice suggested development of atrial defects without any secondary effects on ventricles.

Just recently, we extended these studies on JDP2 mice, starting with JDP2 overexpression in adult mice at the age of 5 weeks. ECGs were recorded on non-anesthetized mice in order to exclude side effects of anesthetics on heart rhythm[22]. Within 4 to 5 weeks of JDP2 overexpression, atrial dilatation and fibrosis, prolongation of conduction times, and episodes of AF became evident. Within this time, reduced expression and phosphorylation of calcium handling proteins (SERCA, RyR2) and connexin 40, as well as a massive increase in pro-inflammatory marker genes, such as MCP1, was detected. Therefore, dysregulated calcium handling and reduced electrical coupling of atrial myocytes likely contribute to atrial dysfunction. Moreover, increased inflammation may provoke arrhythmias, since a role of pro-inflammatory macrophages in the pathogenesis of AF has recently been described[23][24]. Many of the characteristics of the atrial remodeling found in JDP2 mice resemble atrial remodeling in human AF, e.g., atrial myocyte hypertrophy, atrial dilatation, increased fibrosis, alterations in connexin expression and atrial conduction, and dysregulation of myocyte calcium handling[25]. Moreover, recent clinical data also suggest a link between inflammation and AF[26].

5. Summary and Conclusions

In summary, studies from transgenic mice have implicated the transcriptional modulator JDP2 in the development of cardiac remodeling culminating in HF and AF. Patient data suggest JDP2 may be a marker for development and progression of HF. Thus, JDP2 emerges as a novel molecular player in cardiac remodeling in HF and AF.

References

1. A Aronheim; E Zandi; H Hennemann; S J Elledge; M Karin; Isolation of an AP-1 repressor by a novel method for detecting protein-protein interactions.. *Molecular and Cellular Biology* **1997**, *17*, 3094-3102, 10.1128/mcb.17.6.3094.
2. Chunyuan Jin; Hideyo Ugai; Jun Song; Takehide Murata; Feuerstein Nili; Kailai Sun; Masami Horikoshi; Kazunari K. Yokoyama; Identification of mouse Jun dimerization protein 2 as a novel repressor of ATF-2. *FEBS Letters* **2001**, *489*, 34-41, 10.1016/s0014-5793(00)02387-5.
3. Chunyuan Jin; Kohsuke Kato; Takahiko Chimura; Takahito Yamasaki; Koji Nakade; Takehide Murata; Hongjie Li; Jianzhi Pan; Mujun Zhao; Kailai Sun; et al.Robert ChiuTakashi ItoKyosuke NagataMasami HorikoshiKazunari K Yokoyama Regulation of histone acetylation and nucleosome assembly by transcription factor JDP2. *Nature Structural & Molecular Biology* **2006**, *13*, 331-338, 10.1038/nsmb1063.
4. Yu-Chang Huang; Shigeo Saito; Kazunari Kzaushige Yokoyama; Histone Chaperone Jun Dimerization Protein 2 (JDP2): Role in Cellular Senescence and Aging. *The Kaohsiung Journal of Medical Sciences* **2010**, *26*, 515-531, 10.1016/s1607-551x(10)70081-4.

5. Ilona Darlyuk-Saadon; Keren Weidenfeld-Baranboim; Kazunari K. Yokoyama; Tsonwin Hai; Ami Aronheim; The bZIP repressor proteins, c-Jun dimerization protein 2 and activating transcription factor 3, recruit multiple HDAC members to the ATF3 promoter. *Biochimica et Biophysica Acta (BBA) - Molecular Cell Research* **2012**, *1819*, 1142-1153, 10.1016/j.bbagrm.2012.09.005.
6. Kenta Maruyama; Masahiro Fukasaka; Alexis Vandenbon; Tatsuya Saitoh; Takumi Kawasaki; Takeshi Kondo; Kazunari K. Yokoyama; Hiroyasu Kidoya; Nobuyuki Takakura; Daron Standley; et al.Osamu TakeuchiShizuo Akira The Transcription Factor Jdp2 Controls Bone Homeostasis and Antibacterial Immunity by Regulating Osteoclast and Neutrophil Differentiation. *Immunity* **2012**, *37*, 1024-1036, 10.1016/j.immuni.2012.08.022.
7. K Nakade; J Pan; A Yoshiki; H Ugai; Makoto Kimura; B Liu; H Li; Y Obata; M Iwama; S Itohara; et al.T MurataK K Yokoyama JDP2 suppresses adipocyte differentiation by regulating histone acetylation. *Cell Death & Differentiation* **2007**, *14*, 1398-1405, 10.1038/sj.cdd.4402129.
8. Dean P. Edwards; Suzanne E. Wardell; Viroj Boonyaratanakornkit; Progesterone receptor interacting coregulatory proteins and cross talk with cell signaling pathways. *The Journal of Steroid Biochemistry and Molecular Biology* **2002**, *83*, 173-186, 10.1016/s0960-0760(02)00265-0.
9. Suzanne E. Wardell; Viroj Boonyaratanakornkit; James S. Adelman; Ami Aronheim; Dean P. Edwards; Jun Dimerization Protein 2 Functions as a Progesterone Receptor N-Terminal Domain Coactivator. *Molecular and Cellular Biology* **2002**, *22*, 5451-66, 10.1128/mcb.22.15.5451-5466.2002.
10. Suzanne E. Wardell; Stanley C. Kwok; Lori Sherman; Robert S. Hodges; Dean P. Edwards; Regulation of the Amino-Terminal Transcription Activation Domain of Progesterone Receptor by a Cofactor-Induced Protein Folding Mechanism. *Molecular and Cellular Biology* **2005**, *25*, 8792-8808, 10.1128/mcb.25.20.8792-8808.2005.
11. Krista K. Hill; Sarah C. Roemer; David N.M. Jones; Mair E.A. Churchill; Dean P. Edwards; A Progesterone Receptor Co-activator (JDP2) Mediates Activity through Interaction with Residues in the Carboxyl-terminal Extension of the DNA Binding Domain. *Journal of Biological Chemistry* **2009**, *284*, 24415-24424, 10.1074/jbc.m109.003244.
12. Shyh-Shin Chiou; Sophie Sheng-Wen Wang; Deng-Chyang Wu; Ying-Chu Lin; Li-Pin Kao; Kung-Kai Kuo; Chun-Chieh Wu; Chee-Yin Chai; Cheng-Lung Steve Lin; Cheng-Yi Lee; et al.Yu-Mei LiaoKenly WuputraYa-Han YangShin-Wei WangChia-Chen KuYukio NakamuraShigeo SaitoHitomi HasegawaNaoto YamaguchiHiroyuki MiyoshiChang-Sheng LinRichard EcknerKazunari K. Yokoyama Control of Oxidative Stress and Generation of Induced Pluripotent Stem Cell-like Cells by Jun Dimerization Protein 2. *Cancers* **2013**, *5*, 959-984, 10.3390/cancers5030959.
13. S Tanigawa; C H Lee; C S Lin; C C Ku; H Hasegawa; S Qin; A Kawahara; Y Korenori; K Miyamori; M Noguchi; et al.L H LeeYing-Chu LinY NakamuraC JinN YamaguchiR EcknerD-X HouK K YokoyamaChang-Shen LinC L Steve Lin Jun dimerization protein 2 is a critical component of the

Nrf2/MafK complex regulating the response to ROS homeostasis. *Cell Death & Disease* **2013**, *4*, e921-e921, 10.1038/cddis.2013.448.

14. Agata Maciejak; Marek Kiliszek; Marcin Michalak; Dorota Tulacz; Grzegorz Opolski; Krzysztof Matlak; Slawomir Dobrzycki; Agnieszka Segiet; Monika Gora; Beata Burzynska; et al. Gene expression profiling reveals potential prognostic biomarkers associated with the progression of heart failure. *Genome Medicine* **2015**, *7*, 1-15, 10.1186/s13073-015-0149-z.
15. Linlin Qiu; Xueqing Liu; Identification of key genes involved in myocardial infarction. *European Journal of Medical Research* **2019**, *24*, 1-24, 10.1186/s40001-019-0381-x.
16. Shiai Wang; Na Cao; Uncovering potential differentially expressed miRNAs and targeted mRNAs in myocardial infarction based on integrating analysis. *Molecular Medicine Reports* **2020**, *22*, 4383-4395, 10.3892/mmr.2020.11517.
17. Jacqueline Heger; Julia Bornbaum; Alona Würfel; Christian Hill; Nils Brockmann; Renáta Gáspár; János Pálóczi; Zoltán V. Varga; Márta Sárközy; Péter Bencsik; et al.Tamás CsontSzilvia TörökBaktybek KojonazarovRalph Theo SchermulyKerstin BönglerMariana ParahulevaPeter FerdinandyRainer SchulzGerhild Euler JDP2 overexpression provokes cardiac dysfunction in mice. *Scientific Reports* **2018**, *8*, 1-10, 10.1038/s41598-018-26052-w.
18. Christian Hill; Alona Würfel; Jacqueline Heger; Bettina Meyering; Klaus-Dieter Schlüter; Martin Weber; Peter Ferdinandy; Ami Aronheim; Rainer Schulz; Gerhild Euler; et al. Inhibition of AP-1 signaling by JDP2 overexpression protects cardiomyocytes against hypertrophy and apoptosis induction. *Cardiovascular Research* **2013**, *99*, 121-128, 10.1093/cvr/cvt094.
19. R. Kalfon; T. Haas; R. Shofti; J.D. Moskovitz; O. Schwartz; E. Suss-Toby; A. Aronheim; c-Jun dimerization protein 2 (JDP2) deficiency promotes cardiac hypertrophy and dysfunction in response to pressure overload. *International Journal of Cardiology* **2017**, *249*, 357-363, 10.1016/j.ijcard.2017.08.074.
20. Izhak Kehat; Ronit Heinrich; Ofer Ben-Izhak; Hiroshi Miyazaki; J. Silvio Gutkind; Ami Aronheim; Inhibition of basic leucine zipper transcription is a major mediator of atrial dilatation. *Cardiovascular Research* **2006**, *70*, 543-554, 10.1016/j.cardiores.2006.02.018.
21. Brian A. Vanderbrink; Caterina Sellitto; Samir Saba; Mark S. Link; Wei Zhu; Munther K. Homoud; N.A. Mark Estes; David L. Paul; Paul J. Wang; Connexin40-deficient mice exhibit atrioventricular nodal and infra-Hisian conduction abnormalities.. *Journal of Cardiovascular Electrophysiology* **2000**, *11*, 1270-1276, 10.1046/j.1540-8167.2000.01270.x.
22. Mariana S. Parahuleva; Jens Kockskämper; Jacqueline Heger; Wolfram Grimm; Anna Scherer; Sarah Bühler; Julian Kreutz; Rainer Schulz; Gerhild Euler; Structural, Pro-Inflammatory and Calcium Handling Remodeling Underlies Spontaneous Onset of Paroxysmal Atrial Fibrillation in JDP2-Overexpressing Mice. *International Journal of Molecular Sciences* **2020**, *21*, 9095, 10.3390/ijms21239095.

23. Zewei Sun; Dongchen Zhou; Xudong Xie; Shuai Wang; Zhen Wang; Wenting Zhao; Hongfei Xu; Liangrong Zheng; Cross-talk between macrophages and atrial myocytes in atrial fibrillation. *Basic Research in Cardiology* **2016**, *111*, 63, 10.1007/s00395-016-0584-z.
24. Florian Leuschner; Matthias Nahrendorf; Novel functions of macrophages in the heart: insights into electrical conduction, stress, and diastolic dysfunction. *European Heart Journal* **2019**, *41*, 989-994, 10.1093/eurheartj/ehz159.
25. Ulrich Schotten; Sander Verheule; Paulus Kirchhof; Andreas Goette; Pathophysiological Mechanisms of Atrial Fibrillation: A Translational Appraisal. *Physiological Reviews* **2011**, *91*, 265-325, 10.1152/physrev.00031.2009.
26. Christopher John Boos; Infection and atrial fibrillation: inflammation begets AF. *European Heart Journal* **2020**, *41*, 1120-1122, 10.1093/eurheartj/ehz953.