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Ganetespib limits ciliation and cystogenesis in autosomal-dominant polycystic kidney disease (ADPKD)

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Abstract

© 2018 FASEB. Autosomal-dominant polycystic kidney disease (ADPKD) is associated with progressive formation of renal cysts, kidney enlargement, hypertension, and typically end-stage renal disease. In ADPKD, inherited mutations disrupt functionofthe polycystins (encoded byPKD1 and PKD2), thus causing loss of a cyst-repressive signal emanating from the renal cilium. Genetic studies have suggested ciliary maintenance is essential for ADPKD pathogenesis. Heat shock protein 90 (HSP90) clients include multiple proteins linked to ciliary maintenance. We determined that ganetespib, a clinical HSP90 inhibitor, inhibited proteasomal repression of NEK8 and the Aurora-A activator trichoplein, rapidly activating Aurora-A kinase and causing ciliary loss in vitro. Using conditional mouse models for ADPKD, we performed long-term (10 or 50 wk) dosing experiments that demonstrated HSP90 inhibition caused durable in vivo loss of cilia, controlled cystic growth, and ameliorated symptoms induced by loss of Pkd1 or Pkd2.Ganetespib efficacy was not increased by combination with 2-deoxy-D-glucose, aglycolysis inhibitor showing some promise for ADPKD. These studies identify a new biologic activity for HSP90 and support a cilia-based mechanism for cyst repression.

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Keywords

Cilia, Heat shock protein 90, PKD1, Polycystins, Renal cyst

References

[1] Torres, V. E., and Harris, P. C. (2009) Autosomal dominant polycystic kidney disease: the last 3 years. Kidney Int. 76, 149-168

[2] Ma, M., Tian, X., Igarashi, P., Pazour, G. J., and Somlo, S. (2013) Loss of cilia suppresses cyst growth in genetic models of autosomal dominant polycystic kidney disease. Nat. Genet. 45, 1004-1012

[3] Harris, P. C., and Torres, V. E. (2009) Polycystic kidney disease. Annu. Rev. Med. 60, 321-337

[4] Chapman, A. B., Torres, V. E., Perrone, R. D., Steinman, T. I., Bae, K. T., Miller, J. P., Miskulin, D. C., Rahbari Oskoui, F., Masoumi, A., Hogan, M. C., Winklhofer, F.T., Braun, W., Thompson, P. A., Meyers, C. M., Kelleher, C., and Schrier, R. W. (2010) The HALT polycystic kidney disease trials: design and implementation. Clin. J. Am. Soc. Nephrol. 5, 102-109

[5] Perrone, R. D., Malek, A. M., and Watnick, T. (2015) Vascular complications in autosomal dominant polycystic kidney disease. Nat. Rev. Nephrol. 11, 589-598

[6] Schrier, R.W., Abebe, K. Z., Perrone, R.D., Torres, V. E., Braun, W.E., Steinman, T. I., Winklhofer, F. T., Brosnahan, G., Czarnecki, P. G., Hogan, M. C., Miskulin, D. C., Rahbari-Oskoui, F. F., Grantham, J. J., Harris, P. C., Flessner, M. F., Bae, K. T., Moore, C. G., and Chapman, A. B.; HALT-PKD Trial Investigators. (2014) Blood pressure in early autosomal dominant polycystic kidney disease. N. Engl. J. Med. 371, 2255-2266

[7] Torres, V. E., Sweeney, W. E., Jr., Wang, X., Qian, Q., Harris, P. C., Frost, P., and Avner, E. D. (2003) EGF receptor tyrosine kinase inhibition attenuates the development of PKD in Han:SPRD rats. Kidney Int. 64, 1573-1579

[8] Nikonova, A. S., Deneka, A. Y., Eckman, L., Kopp, M. C., Hensley, H. H., Egleston, B. L., and Golemis, E. A. (2015) Opposing effects of inhibitors of Aurora-A and EGFR in autosomal-dominant polycystic kidney disease. Front. Oncol. 5, 228

[9] Rowe, I., Chiaravalli, M., Mannella, V., Ulisse, V., Quilici, G., Pema, M., Song, X.W., Xu, H., Mari, S., Qian, F., Pei, Y., Musco, G., and Boletta, A. (2013) Defective glucose metabolism in polycystic kidney disease identifies a new therapeutic strategy. Nat. Med. 19, 488-493

[10] Serra, A. L., Poster, D., Kistler, A. D., Krauer, F., Raina, S., Young, J., Rentsch, K. M., Spanaus, K. S., Senn, O., Kristanto, P., Scheffel, H., Weishaupt, D., and Wüthrich, R. P. (2010) Sirolimus and kidney growth in autosomal dominant polycystic kidney disease. N. Engl. J. Med. 363, 820-829

[11] Sweeney, W.E., Jr., vonVigier, R.O., Frost, P., and Avner, E.D. (2008) Src inhibition ameliorates polycystic kidney disease. J. Am. Soc. Nephrol. 19, 1331-1341

[12] Seeger-Nukpezah, T., Proia, D. A., Egleston, B. L., Nikonova, A. S., Kent, T., Cai, K. Q., Hensley, H. H., Ying, W., Chimmanamada, D., Serebriiskii, I. G., and Golemis, E. A. (2013) Inhibiting the HSP90 chaperone slows cyst growth in a mouse model of autosomal dominant polycystic kidney disease. Proc. Natl. Acad. Sci. USA 110, 12786-12791

[13] Nikonova, A. S., Plotnikova, O. V., Serzhanova, V., Efimov, A., Bogush, I., Cai, K. Q., Hensley, H. H., Egleston, B. L., Klein-Szanto, A., Seeger-Nukpezah, T., and Golemis, E. A. (2014) Nedd9 restrains renal cystogenesis in Pkd1 mice. Proc. Natl. Acad. Sci. USA 111, 12859-12864

[14] Pugacheva, E. N., Jablonski, S. A., Hartman, T. R., Henske, E. P., and Golemis, E. A. (2007) HEF1-dependent Aurora A activation induces disassembly of the primary cilium. Cell 129, 1351-1363

[15] Plotnikova, O. V., Nikonova, A. S., Loskutov, Y. V., Kozyulina, P. Y., Pugacheva, E.N., and Golemis, E. A. (2012) Calmodulin activation of Aurora-A kinase (AURKA) is required during ciliary disassembly and in mitosis. Mol. Biol. Cell 23, 2658-2670

[16] Jhaveri, K., and Modi, S. (2015) Ganetespib: research and clinical development. Onco Targets Ther. 8, 1849-1858

[17] Socinski, M. A., Goldman, J., El-Hariry, I., Koczywas, M., Vukovic, V., Horn, L., Paschold, E., Salgia, R., West, H., Sequist, L. V., Bonomi, P., Brahmer, J., Chen, L.C., Sandler, A., Belani, C. P., Webb, T., Harper, H., Huberman, M., Ramalingam, S., Wong, K.K., Teofilovici, F., Guo, W., and Shapiro, G. I. (2013) A multicenter phase II study of ganetespib monotherapy in patients with genotypically defined advanced non-small cell lung cancer. Clin. Cancer Res. 19, 3068-3077

[18] Wheway, G., Schmidts, M., Mans, D. A., Szymanska, K., Nguyen, T. T., Racher, H., Phelps, I. G., Toedt, G., Kennedy, J., Wunderlich, K. A., Sorusch, N., Abdelhamed, Z. A., Natarajan, S., Herridge, W., van Reeuwijk, J., Horn, N., Boldt, K., Parry, D. A., Letteboer, S. J. F., Roosing, S., Adams, M., Bell, S. M., Bond, J., Higgins, J., Morrison, E. E., Tomlinson, D. C., Slaats, G. G., van Dam, T. J. P., Huang, L., Kessler, K., Giessl, A., Logan, C. V., Boyle, E.A., Shendure, J., Anazi, S., Aldahmesh, M., Al Hazzaa, S., Hegele, R. A., Ober, C., Frosk, P., Mhanni, A. A., Chodirker, B.N., Chudley, A. E., Lamont, R., Bernier, F. P., Beaulieu, C.L., Gordon, P., Pon, R. T., Donahue, C., Barkovich, A. J., Wolf, L., Toomes, C., Thiel, C. T., Boycott, K.M., McKibbin, M., Inglehearn, C. F., Stewart, F., Omran, H., Huynen, M. A., Sergouniotis, P. I., Alkuraya, F. S., Parboosingh, J. S., Innes, A. M., Willoughby, C. E., Giles, R. H., Webster, A. R., Ueffing, M., Blacque, O., Gleeson, J.G., Wolfrum, U., Beales, P.L., Gibson, T., Doherty, D., Mitchison, H. M., Roepman, R., and Johnson, C. A.; UK10K Consortium University of Washington Center for Mendelian Genomics. (2015) An siRNA-based functional genomics screen for the identification of regulators of ciliogenesis and ciliopathy genes. Nat. Cell Biol. 17, 1074-1087

[19] Kim, J. H., Ki, S. M., Joung, J. G., Scott, E., Heynen-Genel, S., Aza-Blanc, P., Kwon, C.H., Kim, J., Gleeson, J.G., and Lee, J.E. (2016) Genome-wide screen identifies novel machineries required for both ciliogenesis and cell cycle arrest upon serum starvation. Biochim. Biophys. Acta 1863(6, 6 Pt A), 1307-1318

[20] Shaheen, R., Szymanska, K., Basu, B., Patel, N., Ewida, N., Faqeih, E., Al Hashem, A., Derar, N., Alsharif, H., Aldahmesh, M. A., Alazami, A. M., Hashem, M., Ibrahim, N., Abdulwahab, F. M., Sonbul, R., Alkuraya, H., Alnemer, M., Al Tala, S., Al-Husain, M., Morsy, H., Seidahmed, M. Z., Meriki, N., Al-Owain, M., AlShahwan, S., Tabarki, B., Salih, M. A., Ciliopathy Working Group, Faquih, T., El-Kalioby, M., Ueffing, M., Boldt, K., Logan, C.V., Parry, D.A., AlTassan, N., Monies, D., Megarbane, A., Abouelhoda, M., Halees, A., Johnson, C. A., and Alkuraya, F. S. (2016) Characterizing the morbid genome of ciliopathies. Genome Biol. 17, 242

[21] Lee, J. E., and Gleeson, J. G. (2011) A systems-biology approach to understanding the ciliopathy disorders. Genome Med. 3, 59

[22] Van Dam, T. J., Wheway, G., Slaats, G. G., SYSCILIA Study Group, Huynen, M. A., and Giles, R. H. (2013) The SYSCILIA gold standard (SCGSv1) of known ciliary components and its applications within a systems biology consortium. Cilia 2, 7

[23] Jensen, L. J., Kuhn, M., Stark, M., Chaffron, S., Creevey, C., Muller, J., Doerks, T., Julien, P., Roth, A., Simonovic, M., Bork, P., and von Mering, C. (2009) STRING 8-a global view on proteins and their functional interactions in 630 organisms. Nucleic Acids Res. 37(Database), D412-D416

[24] Echeverría, P. C., Bernthaler, A., Dupuis, P., Mayer, B., and Picard, D. (2011) An interaction network predicted from public data as a discovery tool: application to the Hsp90 molecular chaperone machine. PLoS One 6, e26044

[25] Taipale, M., Krykbaeva, I., Koeva, M., Kayatekin, C., Westover, K. D., Karras, G. I., and Lindquist, S. (2012) Quantitative analysis of HSP90-client interactions reveals principles of substrate recognition. Cell 150, 987-1001

[26] Piontek, K., Menezes, L. F., Garcia-Gonzalez, M. A., Huso, D. L., and Germino, G. G. (2007) A critical developmental switch defines the kinetics of kidney cyst formation after loss of Pkd1. Nat. Med. 13, 1490-1495

[27] Piontek, K. B., Huso, D. L., Grinberg, A., Liu, L., Bedja, D., Zhao, H., Gabrielson, K., Qian, F., Mei, C., Westphal, H., and Germino, G. G. (2004) A functional floxed allele of Pkd1 that can be conditionally inactivated in vivo. J. Am. Soc. Nephrol. 15, 3035-3043

[28] Smithline, Z.B., Nikonova, A. S., Hensley, H. H., Cai, K.Q., Egleston, B. L., Proia, D. A., Seeger-Nukpezah, T., and Golemis, E. A. (2014) Inhibiting heat shockprotein 90 (HSP90) limits the formation of liver cysts induced by conditional deletion of Pkd1 in mice. PLoS One 9, e114403

[29] Rasband, W. S. (1997-2009) ImageJ. National Institutes of Health, Bethesda, Maryland

[30] Reichardt, W., Romaker, D., Becker, A., Buechert, M., Walz, G., and von Elverfeldt, D. (2009) Monitoring kidney and renal cyst volumes applying MR approaches on a rapamycin treated mouse model of ADPKD. MAGMA 22, 143-149

[31] Lee, Y. R., and Lee, K. B. (2006) Reliability of magnetic resonance imaging formeasuring the volumetric indices inautosomal-dominant polycystic kidney disease: correlation with hypertension and renal function. Nephron Clin. Pract. 103, c173-c180

[32] Shults, J., Ratcliffe, S. J., and Leonard, M. (2007) Improved generalized estimating equation analysis via xtqls for implementation of quasi-least squares in Stata. Stata J. 7, 147-166

[33] Shillingford, J.M., Murcia, N. S., Larson, C.H., Low, S. H., Hedgepeth, R., Brown, N., Flask, C. A., Novick, A. C., Goldfarb, D. A., Kramer-Zucker, A., Walz, G., Piontek, K. B., Germino, G. G., and Weimbs, T. (2006) The mTOR pathway is regulated by polycystin-1, and its inhibition reverses renal cystogenesis in polycystic kidney disease. Proc. Natl. Acad. Sci. USA 103, 5466-5471

[34] Nicholls, D. G., Darley-Usmar, V. M., Wu, M., Jensen, P. B., Rogers, G. W., and Ferrick, D. A. (2010) Bioenergetic profile experiment using C2C12 myoblast cells. J. Vis. Exp. 46, 2511

[35] Wu, Z., Gholami, A. M., and Kuster, B. (2012) Systematic identification of the HSP90 candidate regulated proteome. Mol. Cell Proteomics 11, M111.016675

[36] Nikonova, A. S., Astsaturov, I., Serebriiskii, I. G., Dunbrack, R. L., Jr., and Golemis, E. A. (2013) Aurora A kinase (AURKA) in normal and pathological cell division. Cell. Mol. Life Sci. 70, 661-687

[37] Kasahara, K., Kawakami, Y., Kiyono, T., Yonemura, S., Kawamura, Y., Era, S., Matsuzaki, F., Goshima, N., and Inagaki, M. (2014) Ubiquitin-proteasome system controls ciliogenesis at the initial step of axoneme extension. Nat. Commun. 5, 5081

[38] Inoko, A., Matsuyama, M., Goto, H., Ohmuro-Matsuyama, Y., Hayashi, Y., Enomoto, M., Ibi, M., Urano, T., Yonemura, S., Kiyono, T., Izawa, I., and Inagaki, M. (2012) Trichoplein and Aurora A block aberrant primary cilia assembly in proliferating cells. J. Cell Biol. 197, 391-405

[39] Cizmecioglu, O., Krause, A., Bahtz, R., Ehret, L., Malek, N., and Hoffmann, I. (2012) Plk2 regulates centriole duplication through phosphorylation-mediated degradation of Fbxw7 (human Cdc4). J. Cell Sci. 125, 981-992

[40] Zalli, D., Bayliss, R., and Fry, A. M. (2012) The Nek8 protein kinase, mutated in thehuman cystic kidney disease nephronophthisis, is both activated and degraded during ciliogenesis. Hum. Mol. Genet. 21, 1155-1171

[41] Ding, X. F., Zhou, J., Hu, Q. Y., Liu, S. C., and Chen, G. (2015) The tumor suppressor pVHL down-regulates never-in-mitosis A-related kinase8 via hypoxia-inducible factors to maintaincilia in humanrenal cancer cells. J. Biol. Chem. 290, 1389-1394

[42] Plotnikova, O.V., Pugacheva, E.N., and Golemis, E.A. (2011) Aurora Akinaseactivity influences calciumsignaling inkidney cells. J. Cell Biol. 193, 1021-1032

[43] Spirli, C., Okolicsanyi, S., Fiorotto, R., Fabris, L., Cadamuro, M., Lecchi, S., Tian, X., Somlo, S., and Strazzabosco, M. (2010) Mammalian target of rapamycin regulates vascular endothelial growth factor-dependent liver cyst growth in polycystin-2-defective mice. Hepatology 51, 1778-1788

[44] Spirli, C., Okolicsanyi, S., Fiorotto, R., Fabris, L., Cadamuro, M., Lecchi, S., Tian, X., Somlo, S., and Strazzabosco, M. (2010) ERK1/2-dependent vascular endothelial growth factor signaling sustains cyst growth in polycystin-2 defective mice. Gastroenterology 138, 360-371 e367

[45] Chiaravalli, M., Rowe, I., Mannella, V., Quilici, G., Canu, T., Bianchi, V., Gurgone, A., Antunes, S., D'Adamo, P., Esposito, A., Musco, G., and Boletta, A. (2016) 2-Deoxy-D-glucose ameliorates PKD progression. J. Am. Soc. Nephrol. 27, 1958-1969

[46] Torres, V. E., Chapman, A. B., Devuyst, O., Gansevoort, R. T., Grantham, J. J., Higashihara, E., Perrone, R.D., Krasa, H. B., Ouyang, J., and Czerwiec, F. S.; TEMPO 3:4 Trial Investigators. (2012) Tolvaptan in patients with autosomal dominant polycystic kidney disease. N. Engl. J. Med. 367, 2407-2418

[47] Watson, M. L., Macnicol, A. M., Allan, P. L., and Wright, A. F. (1992) Effects of angiotensin converting enzyme inhibition in adult polycystic kidney disease. Kidney Int. 41, 206-210

[48] Torres, V. E., Abebe, K. Z., Chapman, A. B., Schrier, R. W., Braun, W. E., Steinman, T. I., Winklhofer, F. T., Brosnahan, G., Czarnecki, P. G., Hogan, M.C., Miskulin, D. C., Rahbari-Oskoui, F. F., Grantham, J. J., Harris, P. C., Flessner, M. F., Moore, C. G., and Perrone, R. D.; HALT-PKD Trial Investigators. (2014) Angiotensin blockade in late autosomal dominant polycystic kidney disease. N. Engl. J. Med. 371, 2267-2276

[49] Wüthrich, R. P., and Mei, C. (2014) Pharmacological management of polycystic kidney disease. Expert Opin. Pharmacother. 15, 1085-1095

[50] Chang, M. Y., and Ong, A. C. (2012) Mechanism-based therapeutics for autosomal dominant polycystic kidney disease: recent progress and future prospects. Nephron. Clin. Pract. 120, c25-c34; discussionc35

[51] Erickson, K. F., Chertow, G. M., and Goldhaber-Fiebert, J. D. (2013) Cost-effectiveness of tolvaptan in autosomal dominant polycystic kidney disease. Ann. Intern. Med. 159, 382-389

[52] Takiar, V., Nishio, S., Seo-Mayer, P., King, J.D., Jr., Li, H., Zhang, L., Karihaloo, A., Hallows, K. R., Somlo, S., and Caplan, M. J. (2011) Activating AMP-activated protein kinase (AMPK) slows renal cystogenesis. Proc. Natl. Acad. Sci. USA 108, 2462-2467

[53] Seeger-Nukpezah, T., Geynisman, D.M., Nikonova, A. S., Benzing, T., and Golemis, E. A. (2015) The hallmarks of cancer: relevance to the pathogenesis of polycystic kidney disease. Nat. Rev. Nephrol. 11, 515-534

[54] Pan, J., Seeger-Nukpezah, T., and Golemis, E. A. (2013) The role of the cilium in normal and abnormal cell cycles: emphasis on renal cystic pathologies. Cell. Mol. Life Sci. 70, 1849-1874

[55] Seeger-Nukpezah, T., and Golemis, E. A. (2012) The extracellular matrix and ciliary signaling. Curr. Opin. Cell Biol. 24, 652-661

[56] Plotnikova, O. V., Pugacheva, E. N., Dunbrack, R. L., and Golemis, E. A. (2010) Rapid calcium-dependent activation of Aurora-A kinase. Nat. Commun. 1, 1-8

[57] Majumder, S., and Fisk, H. A. (2013) VDAC3 and Mps1 negatively regulate ciliogenesis. Cell Cycle 12, 849-858

[58] Kim, S., Lee, K., Choi, J. H., Ringstad, N., and Dynlacht, B. D. (2015) Nek2 activation of Kif24 ensures cilium disassembly during the cell cycle. Nat. Commun. 6, 8087

[59] Outeda, P., Huso, D. L., Fisher, S.A., Halushka, M.K., Kim, H., Qian, F., Germino, G. G., and Watnick, T. (2014) Polycystin signaling is required for directed endothelial cell migration and lymphatic development. Cell Rep. 7, 634-644

[60] Grantham, J. J., and Torres, V. E. (2016) The importance of total kidney volume in evaluating progression of polycystic kidney disease. Nat. Rev. Nephrol. 12, 667-677

[61] Lilja, A., Weeden, C.E., McArthur, K., Nguyen, T., Donald, A., Wong, Z.X., Dousha, L., Bozinovski, S., Vlahos, R., Burns, C. J., Asselin-Labat, M.L., and Anderson, G. P. (2015) HSP90 inhibition suppresses lipopolysaccharide-induced lung inflammation in vivo. PLoS One 10, e0114975