

It is worth mentioning that development of another congenic strain, **BN-Lx.SHR4** double congenic, is near to completion. This strain combines the RNO4 differential segment from **SHR** and the RNO8 differential segment from **PD/Cub** on the **BN/Cub** genetic background. The preliminary metabolic profiling of this congenic strain supports the results presented herein, the dyslipidemia and impaired glucose tolerance being more aggravated than in single congenics, **BN-Lx** and **BN.SHR4**, but still of a lesser extent than in the **BN-Lx 1K** triple congenic strain. But since the total genome scan revealed several chromosomal regions with residual heterozygosity, it is yet impossible to draw any definite conclusions.

In the process of deciphering the genetic determination of IRS, the data presented in this study provide a closer look and proof of engagement of three defined regions of the rat genome, which will be further studied in a more detailed fashion using the set of congenic strains.

### Acknowledgments

We thank Ms. Marie Uxová, Zdena Kopecká and Michaela Janků for their technical assistance.

### References

- Aitman, T. J., Glazier, A. M., Wallace, C. A., Cooper, L. D., Norsworthy, P. J., Wahid, F. N., Al-Majali, K. M., Trembling, P. M., Mann, C. J., Shoulders, C. C., Graf, D., St-Lezin, E., Kurtz, T. W., Křen, V., Pravenec, M., Ibrahimi, A., Abumrad, N. A., Stanton, L. W., Scott, J. (1999) Identification of Cd36 (FAT) as an insulin-resistance gene causing defective fatty acid and glucose metabolism in hypertensive rats. *Nat. Genet.* **21**, 76-83.
- Billingham, R. E., Silvers, W. K. (1959) Inbred animals and tissue transplantation immunity. *Transplant. Bull.* **6**, 399-406.
- Bray, G. A. (1999) The Zucker-fatty rat: a review. *Fed. Proc.* **36**, 148-153.
- Duverger, N., Tremp, G., Caillaud, J. M., Emmanuel, F., Castro, G., Fruchart, J. C., Steinmetz, A., Deneffe, P. (1996) Protection against atherogenesis in mice mediated by human apolipoprotein A-IV. *Science* **273**, 966-968.
- Febbraio, M., Hajjar, D. P., Silverstein, R. L. (2001) CD36: a class B scavenger receptor involved in angiogenesis, atherosclerosis, inflammation, and lipid metabolism. *J. Clin. Invest.* **108**, 785-791.
- Fisher, R. M., Burke, H., Nicaud, V., Ehnholm, C., Humphries, S. E. (1999) Effect of variation in the apo A-IV gene on body mass index and fasting and postprandial lipids in the European Atherosclerosis Research Study II. *J. Lipid Res.* **40**, 287-94.
- Gauguier, D., Froguel, P., Parent, V., Bernard, C., Bihoreau, M. T., Portha, B., James, M. R., Penicaud, L., Lathrop, M., Ktorza, A. (1996) Chromosomal mapping of genetic loci associated with non-insulin dependent diabetes in the GK rat. *Nat. Genet.* **12**, 38-43.
- Goto, Y., Kakizaki, M., Masaki, N. (1975) Spontaneous diabetes produced by selective breeding of normal Wistar rats. *Proc. Jpn. Acad.* **51**, 80-85.
- Hellerstein, M. K. (2002) Carbohydrate-induced hypertriglyceridemia: modifying factors and implications for cardiovascular risk. *Curr. Opin. Lipidol.* **13**, 33-40.
- Kawano, K., Hirashima, P., Mori, S., Kurosumi, P., Saitoh, Y. (1991) A new rat strain with non insulin dependent diabetes mellitus, „OLETF“. *Rat News Lett.* **25**, 22-26.
- Kawano, K., Hirashima, P., Mori, S., Kurosumi, P., Natori, T. (1992) Spontaneous long-term hyperglycemia with diabetic complication: Otsuka-Long-Evans Tokushima Fatty (OLETF) strain. *Diabetes* **41**, 1422-1428.
- Ito, Y., Azrolan, N., O'Connell, A., Walsh, A., Breslow, J. L. (1990) Hypertriglyceridemia as a result of human apo CIII gene expression in transgenic mice. *Science* **249**, 790-793.
- Jacob, H. J., Kwitek, A. E. (2002) Rat genetics: attaching physiology and pharmacology to the genome. *Nat. Rev. Genet.* **3**, 33-42.
- Křen, V. (1975) Genetics of the polydactyly-luxate syndrome in the Norway rat, *Rattus norvegicus*. *Acta Univ. Carol. Med. Praha (Monogr.)* **68**, 1-103.
- Křen, V., Křenová, D., Pravenec, M., Zdobinská, M. (1995) Chromosome 8 congenic strains: tools for genetic analysis of limb malformation, plasma triglycerides, and blood pressure in the rat. *Folia Biol. (Praha)* **41**, 284-293.
- Křen, V., Křenová, D., Bílá, V., Zdobinská, M., Zídek, V., Pravenec, M. (1996) Recombinant inbred and congenic strains for mapping of genes that are responsible for spontaneous hypertension and other risk factors of cardiovascular disease. *Folia Biol. (Praha)* **42**, 155-158.
- Norman, R. A., Thompson, D. B., Foroud, T., Garvey, W. T., Bennett, P. H., Bogardus, C., Ravussin, E. (1997) Genomewide search for genes influencing percent body fat in Pima Indians: suggestive linkage at chromosome 11q21-q22. *Am. J. Hum. Genet.* **60**, 166-173.
- Norman, R., Tataranni, P., Pratley, R., Thompson, D. B., Hanson, R. L., Prochazka, M., Baier, L., Ehm, M. G., Sakul, H., Foroud, T., Garvey, W. T., Burns, D., Knowler, W. C., Bennett, P. H., Bogardus, C., Ravussin, E. (1998) Autosomal genomic scan for loci linked to obesity and energy metabolism in Pima Indians. *Am. J. Hum. Genet.* **62**, 659-68.
- Okamoto, K., Aoki, K. (1963) Development of a strain of spontaneously hypertensive rats. *Jpn. Circ. J.* **27**, 282-293.
- Okuno, S., Watanabe, T. K., Ono, T., Yamasaki, Y., Goto, Y., Miyao, H., Asai, T., Kanemoto, N., Oga, K., Mizoguchi-Miyakita, A., Takagi, T., Takahashi, E., Nakamura, Y., Tanigami, A. (1999) Genetic determinants of plasma triglyceride levels in (OLETF x BN) x OLETF backcross rats. *Genomics* **62**, 350-355.
- Parks, E. J., Hellerstein, K. (2000) Carbohydrate-induced hypertriglycerolemia: historical perspective and review of biological mechanisms. *Am. J. Clin. Nutr.* **71**, 412-433.
- Pennacchio, L. A., Olivier, M., Hubacek, J. A., Cohen J. C., Cox, D. R., Fruchart, J.-C., Krauss, R. M., Rubin, E. M. (2001) An apolipoprotein influencing triglycerides in humans and mice revealed by comparative sequencing. *Science* **294**, 169-173.
- Pravenec, M., Klír, P., Křen, V., Zicha, J., Kuneš, J. (1989) An analysis of spontaneous hypertension in spontaneously hypertensive rats by means of new recombinant inbred strains. *J. Hypertens.* **3**, 217-221.
- Pravenec, M., Landa, V., Zídek, V., Musilová A., Křen, V., Kazdová, L., Aitman T. J., Glayier A. M., Ibrahimi A.,

- Abumrad, N. A., Qi, N., Wang, J., St. Lezin, E., Kurtz, T. W. (2001) Transgenic rescue of defective Cd36 ameliorates insulin resistance in spontaneously hypertensive rats. *Nat. Genet.* **27**, 156-158.
- Rapp, J. P. (2000) Genetic analysis of inherited hypertension in the rat. *Physiol. Rev.* **80**, 135-172.
- Reaven, G. M. (1988) Banting lecture: role of insulin resistance in human disease. *Diabetes* **37**, 1595-1607.
- Shachter, N. S. (2001) Apolipoproteins C-I and C-III as important modulators of lipoprotein metabolism. *Curr. Opin. Lipidol.* **12**, 297-304.
- Šedová, L., Kazdová, L., Šeda, O., Křenová, D., Křen, V. (2000a) Rat inbred PD/Cub strain as a model of dyslipidemia and insulin resistance. *Folia Biol. (Praha)* **46**, 99-106.
- Šedová, L., Křenová, D., Kemlink, D., Pravenec, M., Křen, V. (2000b) Mapping and phenotypic manifestation of the Lx mutation in the SHR-Lx congenic substrains. *Rat Genome* **6**, 72.
- van der Vliet, H. N., Sammels, M. G., Leegwater, A. C. J., Levels, J. H. M., Reitsma, P. H., Boers, W., Chamuleau, R. A. F. M. (2001) Apolipoprotein A-V: a novel apolipoprotein associated with an early phase of liver regeneration. *J. Biol. Chem.* **276**, 44512-44520.
- Vergnes, L., Baroukh, N., Ostos, M. A., Castro, G., Duverger, N., Nanjee, M. N., Najib, J., Fruchart, J.-C., Miller, N. E., Zakin, M. M., Ochoa, A. (2000) Expression of human apolipoprotein A-I/C-III/A-IV gene cluster in mice induces hyperlipidemia but reduces atherogenesis. *Arterioscler. Thromb. Vasc. Biol.* **20**, 2267-2274.
- Vrána, A., Kazdová, L. (1990) The hereditary hypertriglyceridemic nonobese rat: an experimental model of human hypertriglyceridemia. *Transplant. Proc.* **22**, 2579.
- Walsh, A., Ito, Y., Breslow, J. L. (1989) High levels of human apolipoprotein A-I in transgenic mice result in increased plasma levels of small high density lipoprotein (HDL) particles comparable to human HDL3. *J. Biol. Chem.* **264**, 6488-6494.
- Zucker, L. M. (1972) Fat mobilization in vitro and in vivo in the genetically obese Zucker rat „fatty“. *J. Lipid. Res.* **13**, 234-243.