Conference

Insights into the PPARγ phosphorylation and its inhibition mechanism.

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Peroxisome proliferator-activated receptor gamma Ligand Binding Domain (PPARγ-LBD) represents a key target for the treatment of type II diabetes and metabolic syndrome. This receptor is the target of thiazolidinediones, a class of antidiabetic drugs, which improve insulin sensitization and regulate glycemia in type 2 diabetes. Unfortunately, despite the beneficial effects of synthetic drugs, their use is associated with serious undesirable side effects[1,2] related to their agonism. By contrast, a promising activation-independent mechanism that involves the inhibition of cyclin-dependent kinase 5 (Cdk5)-mediated PPARγ phosphorylation (CMPF) has been related to the insulin-sensitizing effects induced by these drugs.[3,4] For this reason, the search for new inhibitors of CMPF represents an opportunity for the development of an improved generation of anti-diabetic drugs acting through this nuclear receptor. Thus, with the aim to identify novel drug-like inhibitors of CMPF capable of interacting with PPARγ but that lack agonist properties we adopted a multi-disciplinary approach, including protein-protein docking, X-ray, NMR, HDX, MD simulations and site-directed mutagenesis to investigate conformational changes in PPARγ that impair the ability of Cdk5 to interact with this nuclear receptor and hence inhibit its phosphorylation.

References

1 M. Bodmer, C. Meier, M. E. Kraenzlin, C. R. Meier, Risk of Fractures with Glitazones, Drug safety 32 (7) (2009) 539–547. doi:10.2165/00002018-200932070-00001.

2 R. W. Nesto, D. Bell, R. O. Bonow, V. Fonseca, S. M. Grundy, E. S. Horton, M. Le Winter, D. Porte, C. F. Semenkovich, S. Smith, et al., Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association, Diabetes care 27 (1) (2004) 256–263. doi:10.2337/diacare.27.1.256.

3 J. H. Choi, A. S. Banks, J. L. Estall, S. Kajimura, P. Boström, D. Laznik, J. L. Ruas, M. J. Chalmers, T. M. Kamenecka, M. Blüher, et al., Anti-diabetic drugs inhibit obesity-linked phosphorylation of PPARγ by Cdk5, Nature 466 (7305) (2010) 451–456. doi:10.1038/nature09291.

4 J. H. Choi, A. S. Banks, T. M. Kamenecka, S. A. Busby, M. J. Chalmers, N. Kumar, D. S. Kuruvilla, Y. Shin, Y. He, J. B. Bruning, et al., Antidiabetic actions of a non-agonist PPARγ ligand blocking Cdk5-mediated phosphorylation, Nature 477 (7365) (2011) 477–481. doi:10.1038/nature10383.

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