(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
25 April 2002 (25.04.2002)

PCT

(10) International Publication Number
WO 02/33063 A1

(51) International Patent Classification[7]: C12N 9/04, 15/53

(21) International Application Number: PCT/KR01/01271

(22) International Filing Date: 26 July 2001 (26.07.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2000/61962 20 October 2000 (20.10.2000) KR

(71) Applicant *(for all designated States except US)*: **TG BIOTECH, INC.** [KR/KR]; 452-2, Sungnae 1-dong, Kangdong-ku, Seoul 134-031 (KR).

(71) Applicant and
(72) Inventor: **HUH, Tae-Lin** [KR/KR]; #255-107 Dongsuh-town Apt. Shinmae-dong, Soosung-ku, Daegu_706-781 (KR).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **KOH, Ho-Jin** [KR/KR]; 17-4, Daehyun 1-dong, Puk-ku, Daegu 702-041 (KR). **CHOI, Myung-Sook** [KR/KR]; #102-203 Gardenheights, Bumuh 4-dong, Soosung-ku, Daegu 706-014 (KR). **JUNG, Un-Ju** [KR/KR]; #206, 112-8 Daehyun 1-dong, Puk-ku, Daegu 702-041 (KR).

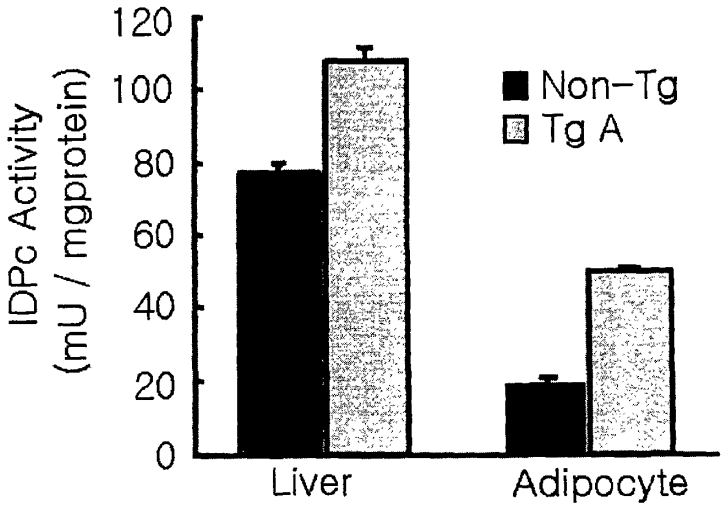
(74) Agent: **LEE, Won-Hee**; Sung-ji Heights II, 8th Floor, 642-16 Yoksam-dong, Kangnam-ku, Seoul 135-080 (KR).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) Title: ISOCITRATE DEHYDROGENASE, GENE THEREOF, AND USE OF THE SAME IN THE TREATMENT OF OBESITY, HYPERLIPIDEMIA, AND FATTY LIVER IN LIPID BIOSYNTHESIS



(57) Abstract: The present invention relates to a cytosolic isocitrate dehydrogenase, its gene, and its use in the treatment of obesity, hyperlipidemia, and fatty liver. The expression of the IDPc gene and the concomitant increase in IDPc level bring about an increase in the cellular level of NADPH, which causes the lipid deposition in adipocytes, leading to obesity and fatty liver. A decrease in the cellular level of NADPH, resulting from the suppression of the gene expression of IDPc, has the effect of inhibiting the lipid deposition in adipocytes. Further, by taking advantage of the suppressive or inhibitory effects of isocitrate dehydrogenase inhibitors, pharmaceutically effective materials for the prophylaxis and treatment of obesity, hyperlipidemia and fatty liver can be developed.

WO 02/33063 A1

Published:
— *with international search report*
— *entirely in electronic form (except for this front page) and available upon request from the International Bureau*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

ISOCITRATE DEHYDROGENASE, GENE THEREOF, AND USE OF THE SAME IN THE TREATMENT OF OBESITY, HYPERLIPIDEMIA, AND FATTY LIVER IN LIPID BIOSYNTHESIS

FIELD OF THE INVENTION

The present invention relates to an isocitrate dehydrogenase which catalyze the production of NADPH necessary for the biosynthesis of lipids, including fatty acids, squalene and cholesterol, and its use in the treatment of metabolic diseases, including obesity, hyperlipidemia and fatty liver. Also, the present invention relates to an isocitrate dehydrogenase gene, fused gene constructs containing the gene, transfectant cells harboring the genes in their genome, and transgenic animals capable of expressing isocitrate dehydrogenase continuously throughout their lifespan.

BACKGROUND OF THE INVENTION

Taking part in the TCA (tricarboxylic acid) cycle, isocitrate dehydrogenase catalyses the oxidative decarboxylation of citric acid into α-ketoglutarate with concurrent production of NADH or NADPH.

In higher animals, isocitrate dehydrogenase

isozymes can be separated into three classes according to their cofactors and locations in the cell: mitochondrial NAD^+-dependent isocitrate dehydrogenase (hereinafter referred to as "IDH"), mitochondrial $NADP^+$-dependent isocitrate dehydrogenase (hereinafter referred to as "IDPm"), and cytoplasmic $NADP^+$-dependent isocitrate dehydrogenase (hereinafter referred to as "IDPc"). Among these isocitrate isoenzymes, IDH has been assumed to play a major role in the oxidative decarboxylation of isocitrate in the tricarboxylic acid cycle (TCA) with concurrent production of α-ketoglutarate and NADH. NADH is used for energy generation through the electron transfer system and α-ketoglutarate is a metabolite used in the synthesis of amino acids such as glutamic acid, glutamine, arginine, and proline, and other biological products. IDH activity is regulated as a control point of the TCA cycle. Therefore, IDH is a key enzyme to regulate not only the TCA cycle, but also energy metabolism, protein biosynthesis and nitrogen metabolism because metabolites of the TCA cycle take part in such metabolisms.

Since its isolation from yeast and pig, IDH has been under study. Yeast IDH is an allosterically regulated enzyme that exists as an octamer composed of two nonidentical subunits IDH1 and IDH2 sharing high homology with each other. IDH1 plays a role in the

regulation of the enzyme activity while IDH2 is responsible for the catalytic activity (Keys, D. A. & McAlister-Henn, L., J. Bacteriol., 172, 4280-4287, 1990). Broken down into three subunits (α, β, γ subunits), swine IDH also exists as an octamer (2(α 2β γ)) in active form.

Found to have bipartite structures, IDPm and IDPc are, however, not known as to their functions. Although both having molecular weight of about 45 kDa with high homology, the two enzymes were identified as different, independent proteins, as analyzed by immunological reaction experiments using polyclonal antibodies (Plaut, G. W. E. et al., Biochem. Biophys. Acta., 760, 300-308, 1983; Fantania, H. R. et al., FEBS, 322, 245-248, 1993). Particularly, IDPm and IDPc are highly tissue-specific. In cardiac muscle tissues, for instance, more than 90 % of total $NADP^+$-dependent isocitrate dehydrogenase exists in mitochondria and the remaining 10 % is found in cytoplasm. In contrast, it is reported that as low as 3 % of the total $NADP^+$-dependent isocitrate dehydrogenase of liver tissues is found in mitochondria while the remaining 97 % exists in cytoplasm (Plaut, G. W. E., Current Topics in Cell Regulation, 2, 1-27, 1983).

As mentioned above, isocitrate dehydrogenase isozymes have been characterized concerning some of

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.