

COMPOSITIONS AND METHODS OF DISEASE DIAGNOSIS AND THERAPY

This application is a continuation-in-part application of U.S. Ser. No. 09/221,222, filed Dec. 23, 1998, which is a continuation-in-part application of U.S. Ser. No. 09/167,750, filed Oct. 7, 1998, which is a continuation-in-part application of U.S. Ser. No. 09/086,047, filed May 28, 1998.

FIELD OF THE INVENTION

The invention relates in general to the discovery of the mechanisms underlying disease.

BACKGROUND OF THE INVENTION

Coronary heart disease, hypertension, non-insulin-dependent diabetes, insulin resistance or -insensitivity and obesity are major causes of ill health in industrial societies. Disturbances of carbohydrate and lipid metabolism are a common feature of those disorders (Evans et al., 1984, *J. Clin. Invest.*, 74: 1515-1525; Ferrannini et al., 1987, *N. Engl. J. Med.*, 317: 350-357; Reaven, 1988a, *Diabetes*, 37: 1595-1607; Hunt et al., 1989, *Arteriosclerosis*, 9: 335-344; Kaplan, 1989, *Arch. Intern. Med.*, 149: 1514-1520; McGarry, 1992, *Science*, 258: 766-770; Cohen et al., 1996, *Science*, 274: 1185-1188; Polonsky et al., 1995, *N. Engl. J. Med.*, 334: 777-783; Reaven et al., 1996, *N. Engl. J. Med.*, 334: 374-381). Specifically, disturbances in carbohydrate- and fatty acid metabolism associated with defects in insulin and catecholamine action are characteristic of non-insulin-dependent diabetes, metabolic Syndrome X, obesity, familial dyslipidemic hypertension and familial combined hyperlipidemia (Reaven, 1988a, supra; Reaven et al., 1988b, *Diabetes*, 37: 1020-1024; Martin and Jensen, 1991, *J. Clin. Invest.*, 88: 609-613; Hunt et al., 1989, supra; Castro Cabezas et al., 1993, *J. Clin. Invest.*, 92: 160-168; Aitman et al., 1997, *Arterioscler. Thromb. Vasc. Biol.*, 17: 748-754; Reynisdottir et al., 1994, *Diabetologia*, 37: 428-435; Reynisdottir et al., 1995, *J. Clin. Invest.*, 95: 2163-2169). These conditions are treatable by modifications of patient lifestyle (e.g., diet and exercise) and/or with medication. If the presence- or risk of developing such a condition is identified early, a therapeutic or prophylactic regimen may be begun before the well-being of the patient has been compromised, either at all or to an appreciable extent.

There is need in the art for methods of diagnosing an individual having a propensity for one or more of heart disease, hypertension, non-insulin-dependent diabetes, metabolic Syndrome X, combined hyperlipidemia and/or obesity.

It has been suggested in the art that certain parasites utilize the CD36 protein as a ligand for infection of the host cell (Oquendo et al., 1989, *Cell* 58:95). An example is *Plasmodium falciparum*, a causative agent of malaria. Thus, hosts that express a variant of CD36 protein, or fail to express CD36, may have a greater resistance to infection by such parasites. A significant fraction of individuals lacking CD36 protein have been identified in populations of Asian and African origin, whose ancestry suggests that the phenotype became commonplace due to selection pressure from frequent malarial infection. Curtis, B. R., and Aster, R. H., 1996, *Transfusion* 36: 331-334.

There is a need in the art for methods of determining resistance or susceptibility to infection by *Plasmodium falciparum*.

It has been suggested that some apparently normal individuals lack GPIV, and thus are at risk of producing anti-

bodies against the protein when they receive blood transfusions. Curtis et al., 1996, supra; Greenwalt et al., 1992, *Blood* 80:1105; Yamamoto et al., 1990, *Blood* 76:1698.

There is a need in the art for detecting CD36 gene mutations that give rise to CD36 deficiency for purposes of tissue screening and donation.

SUMMARY OF THE INVENTION

The invention provides a method of identifying an agent which modulates a defect in insulin action and/or glucose metabolism and/or fatty acid metabolism and/or catecholamine action, the method comprising the step of determining in an assay system whether an activity of a gene regulating insulin action and/or glucose metabolism and/or fatty acid metabolism and/or catecholamine action is altered in the presence of a candidate modulator, wherein alteration of the activity of the gene in the presence of the candidate modulator is indicative of efficacy of the candidate modulator in modulating defective insulin action and/or glucose metabolism and/or fatty acid metabolism and/or catecholamine action.

As used herein, the term "agent" refers to a biochemical substance selected from the group that includes, but is not limited to, proteins, peptides or amino acids; nucleic acids such as DNA, such as full-length genes or fragments thereof derived from genomic, cDNA or artificial coding sequences, gene regulatory elements, RNA, including mRNA, tRNA, ribosomal RNA, ribozymes and antisense RNA, oligonucleotides and oligoribonucleotides, deoxyribonucleotides and ribonucleotides; carbohydrates; lipids; proteoglycans; such agents may exist as isolated (purified) compounds or in crude mixtures, such as in a tissue, cell or cell lysate. In addition, such agents may be naturally occurring or may be synthetic. The term "agent" additionally refers to small molecules, such as organic and inorganic compounds.

As used herein, the term "gene" refers to a nucleic acid sequence which comprises one or more of an exon, which exon may encode a protein or an RNA molecule, an intron, a 5'-untranslated region, a 3'-untranslated region and a regulatory sequence, which regulatory sequence may be located either 5' to- or 3' of the exon, either in a transcribed- or a non-transcribed sequence.

As used herein with regard to the expression or activity of a gene or protein, the term "modulate" refers to the effect of an agent (such as a drug or other pharmacological composition) or condition (such as an environmental change or a genetic mutation) either to stimulate, enhance or otherwise increase- or to inhibit, repress, depress or otherwise decrease expression of that gene (whether expression is detected via the RNA, protein, or gene product activity) or protein by at least 10% relative to its basal level of expression. An agent which modulates the expression or activity of a gene or protein is herein referred to as a "modulator". The percent change in expression or activity relative to the basal level or to a control which has not been contacted with a modulator or candidate modulator may be greater than 10%, such as 20-50%, or 75-100%. Alternatively, a modulator may effect a change in activity or expression of greater than 100%, for example 2- to 10-fold, 20- to 100-fold, 1000-fold, or even 10,000- to-100,000-fold above or below the basal level of expression or activity or that observed in a control which has not received or been contacted by the modulator (i.e., an untreated control).

As used herein in reference to the expression or activity of a gene or protein, the term "basal level" refers to the level of expression or activity of that gene or protein in an