

These mice provide a useful mechanistic model for dissecting out the complex interactions of TCR signalling. Additionally, the mice are useful for evaluation of therapeutics directed at specific classes of diseases (Th1 or Th2) and the utility of potential global Tec kinase inhibitors.

A Mouse Model for Type 2 Diabetes

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Diabetes affects over 120 million people worldwide (16 million in the US) and is a major health problem with associated health costs estimated at almost \$100 billion dollars. Type 2 diabetes affects as many as 10% of the population of the Western World (with 15 million patients in the U.S. alone) and arises from a heterogeneous etiology, with secondary effects from environmental influences. Risk factors for type 2 diabetes include obesity, high blood pressure, high triglycerides and age. Type 2 diabetes is an active area for drug development and there continues to be a need for novel animal models and research tools to aid in the discovery and development of new, more efficient and cost-effective therapeutics.

Peripheral insulin resistance and impaired insulin action are the primary characteristics of type 2 diabetes. The first observable defect in this major disorder occurs in muscle, where glucose disposal in response to insulin is impaired. In an effort to study the progression of diabetes, researchers at NIDDK have developed a transgenic mouse strain (MKR) with a dominant-negative insulin-like growth factor-I receptor (KR-IGF-IR) specifically targeted to skeletal muscle (Genes & Development (2001) 15, 1926-1934). Expression of KR-IGF-IR resulted in the formation of hybrid receptors between the mutant and the endogenous IGF-I and insulin receptors, thereby abrogating the normal function of these receptors and leading to insulin resistance. Pancreatic β -cell dysfunction developed at a relative early age, resulting in diabetes.

One of the great advantages of the MKR mouse over other mouse models is the early onset of the disease phenotype as seen by insulin resistance (as early as 4 weeks), fasting hyperglycemia (from 5 weeks) and abnormal glucose tolerance (at 7-12 weeks). The MKR mice provide an extremely useful model for the study of type 2 diabetes, its pathogenesis and potential new therapies.

A Tet-Regulated Mouse Model for Cataract

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Cataract is the most common cause of blindness worldwide, with an estimated 25 million blind and 119 million visually impaired individuals worldwide. Over 20 million adults in the U.S. alone are currently diagnosed with cataracts making this disease a major health concern. The incidence of cataract increases with age and a number of etiologic factors have been proposed in the pathogenesis of age-related cataract in humans including genetic factors, environmental factors and metabolic and biochemical changes in the crystalline lens. Ultraviolet radiation exposure and oxidative injury to the lens has been considered by some to be one of the most important factors in cataractogenesis. The present therapy of choice for cataract is laser surgery.

Experimental investigation of human age-related cataract is hindered by a lack of available animal models of cataract. Several laboratory mice strains with heritable cataracts have been studied including the Nakona, Frasier and the Philly mouse strains. An animal model with a predictable phenotype of cataract, particularly one with a pathogenesis relating to oxidative injury to the lens (the proposed central factor in human-related cataract) would be of great value to ophthalmic researchers and in the development of pharmacological agents for delaying or preventing cataract.

Researchers at the NIEHS have developed a transgenic mouse model in which the DNA repair gene DNA polymerase β (β -pol) is highly over-expressed in the lens epithelial cells of the eye (DNA Repair (2003) 609-622). A bicistronic tetracycline-responsive transgenic system was used to over-express β -pol in mice. Over-expression of β -pol in the lens epithelium results in the early onset of severe cortical cataract with cataractogenesis beginning within 4 days after birth. In utero and post-natal suppression of transgenic Flag- β -pol-expression by doxycycline administration completely prevents cataract formation through adulthood, yet cataract is subsequently observed following removal of doxycycline and re-expression of the transgene. This predictable and regulated onset of cataract makes this mouse an ideal animal model both for evaluating new therapeutics for delaying or preventing cataract as well as for understanding the

mechanisms responsible for cataract formation.

A Mouse Model for Human Osteoarthritis

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Osteoarthritis (OA) is the most common form of arthritis and affects more than 20 million Americans, costing billions of dollars in health care annually. Osteoarthritis is caused by the breakdown of joint cartilage, leading to a loss of the cartilage "cushion" between the bones of the joints. Risk factors associated with OA include age, obesity, traumatic injury and overuse due to sports or occupational stresses. There is no cure for OA and current treatments are directed at the symptomatic relief of pain, and at improving and maintaining joint function. There remains, however, a critical need both to develop OA treatments that focus on slowing down the degenerative process of the disease and for validated animal models to test these new treatments. NIH scientists at the NIDCR have generated a mouse model for osteoarthritis (FASEB J. (2002) 16, 673-680) that fills one part of this important gap.

The mouse model is a double knockout mouse that lacks biglycan and fibromodulin, two members of the small leucine-rich proteoglycan family, and that spontaneously develops OA. All the hallmarks of human osteoarthritis are present, including: progressive degeneration of the articular cartilage from early fibrillation to complete erosion, subchondral sclerosis, an absence of inflammation and development of osteophytes and cysts. Advantages over the existing models for osteoarthritis include: high phenotypic penetrance, early onset (at 1-2 months) and a rapid disease progression (between 3-6 months) which can be accelerated by moderate levels of exercise, such as treadmill running. These properties, combined with a normal life span, make the biglycan/fibromodulin-deficient mouse an ideal animal model for evaluating new drugs and treatments for osteoarthritis.

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