S-2-5

MONOCLONAL ANTIBODIES AND MUTAGENESIS AS PROBES OF INSULIN ACTION, INTERNALIZATION AND DEGRADATION

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A variety of monoclonal antibodies to the insulin receptor, insulin-degrading enzymes and potential substrates for the insulin receptor kinase have been used to elucidate the steps involved in mediating various responses to insulin as well as the subsequent events in insulin's interactions with cells. In addition, various cell lines expressing transfected human insulin receptor cDNAs encoding for normal receptor as well as several mutated receptors were utilized. The tyrosine kinase activity of the receptor was found to be required for insulin to induce various metabolic responses in several cell types as well as the translocation of the receptor to an intracellular site. The subsequent steps in insulin action may include the interaction of the receptor with a GTP-binding protein of Mr = 21,000, called ras p21. Additional studies are in progress to further define the role of ras p21 and other substrates of the insulin receptor kinase in mediating the biological responses to insulin and the insulin-like growth factors.

S-3-1

THE INFLUENCE OF GENETIC BACKGROUND ON SUSCEPTIBILITY TO STREPTOZOTOCIN-INDUCED AUTOIMMUNE DIABETES IN MICE

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The influence of genetic background on the susceptibility to streptozotocin-induced (40 mg/kg, i.p., 5 days) diabetes was studied by comparing the susceptibilities of various congenic resistant and recombinant strains with a B10 background. In congenic resistant strains, mice from strains B10. ($H\text{-}2^b$) and B10.BR ($H\text{-}2^k$) showed high incidences of diabetes in response to streptozotocin treatment. However, mice from strains B10.D2 ($H\text{-}2^d$) and B10.S ($H\text{-}2^s$) showed low incidences of diabetes, suggesting that the haplotypes b and k are high-susceptibility alleles and that d and s are low-susceptibility alleles. In congenic recombinant strains, mice with the same haplotype on the K, E, S and D loci in the H-2 complex showed different susceptibilities, indicating that the diabetic susceptibility genes are located outside the K, E, S and D loci. The results suggested that genes coding for susceptibility to diabetes are located in the A locus within the H-2 complex.