the arcuate nucleus and ventromedial hypothalamus to increase appetite (100). Vaccination of adult rats with ghrelin peptides conjugated to keyhole limpet hemocyanin-induced antibodies that bound the circulating active Ser-3-(n-octanoyl) form of ghrelin and decreased feeding efficiency, relative adiposity, and body weight gain compared with control rats (101).

GIP is an incretin produced by K cells in the duodenum and upper jejunum, which stimulates insulin biosynthesis and secretion (102). Recently, GIP receptor-deficient mice were shown to be completely protected from diet-induced obesity (103), suggesting that blockade of GIP signaling could be a therapeutic strategy for the treatment of obesity. Vaccination of mice with GIP peptides covalently attached to virus-like particles induced high titers of specific antibodies and efficiently reduced body weight gain in animals fed a high-fat human diet (104). Importantly, despite the incretin action of GIP, vaccinated mice were not glucose intolerant. Further preclinical safety/toxicology studies will be required before this strategy is translated to humans.

Insulin Resistance and Type 2 Diabetes

Tissue resistance to the action of insulin is a characteristic of obesity and contributes to the pathogenesis of T2D. Many investigators have shown that insulin resistance is associated with chronic, low-grade innate immune inflammation in multiple tissues (105,106) that resolves with weight loss (107,108). Metabolic stress in adipocytes associated with the accumulation of fat induces release of chemoattractants including monocyte chemoattractant protein-1 (MCP-1 or CCL2), which recruits circulating monocytes to adipose tissue and promotes their differentiation into macrophages (109). In adipose tissue of obese mice, the major source of inflammatory mediators, macrophages, are hypothesized to underlie insulin resistance (110,111). Innate immunity may also impair pancreatic β-cell function in T2D. Islets from humans with T2D contain more macrophages and secrete more proinflammatory cytokines than normal islets (112). The role of inflammation in insulin resistance and T2D is supported by trials of anti-inflammatory agents. Salicylates were documented to improve glucose tolerance over a century ago (113,114). RA patients who underwent treatment with TNF-α monoclonal antibody exhibited improved insulin sensitivity (115) and recombinant IL-1Ra was shown to improve insulin secretion and glucose tolerance in T2D (116). Antagonists of chemokine receptor 2 (CCR2), the receptor for MCP-1, including small molecules in commercial development, have shown promise in reversing fat accumulation, insulin resistance, and glucose intolerance in mice (117). Although one or more specific cytokines or chemokines have not been proven to fully account for insulin resistance, autovaccination against candidate mediators is an obvious potential therapeutic strategy.

Atherosclerosis

Many studies have demonstrated a role for innate and adaptive immunity in atherosclerosis (118,119). The rationale for vaccination in atherosclerosis (120) is therefore the same as in obesity-insulin resistance diabetes; indeed, a continuum of inflammatory mechanisms leads from this ''metabolic syndrome'' to its vascular complications. Moreover, it is likely that drugs used for cardiovascular prophylaxis, including cholesterol-lowering agents, have significant anti-inflammatory effects critical for their efficacy.

In rodent models and humans with atherosclerosis, oxidized low-density lipoproteins (oxLDL), heat shock protein (HSP) 60/65 and β-2 glycoprotein 1 have been identified as targets of humoral and cellular immunity, and protection has been afforded by vaccination with these autoantigens. Autoantibodies against malondialdehyde (MDA)-modified lysine, an epitope in oxLDL, occur naturally and are present as immune complexes with oxLDL in atherosclerotic lesions. Atherosclerosis-prone LDL receptor-deficient rabbits vaccinated with homologous MDA-LDL generated high titers of antibodies with similar specificity to the naturally occurring autoantibodies and exhibited significant reduction of aortic tree atherosclerotic lesions after 6.5 months compared with controls (121). It has been proposed that pneumococcal vaccination decreases atherosclerosis by generating IgM antibodies that cross-react with oxLDL (122), but this is disputed in humans (123). Separately, influenza infection has been associated with an increased risk of acute cardiac infarction, and influenza vaccination has been reported to reduce this risk (124), but the protective effect of vaccination has been questioned (125). Autoantibodies to apolipoprotein (apo) B-100 peptides are present in humans and have been shown to be associated with decreased cardiovascular risk. To determine if apo B-100 peptide vaccines are protective in mice expressing human apo B-100, LDL receptor-deficient/human apo B-100 transgenic mice were injected subcutaneously (SC) with native human apo B-100 peptides in alum at 6, 9, and 11 weeks of age (126). Treatment significantly reduced atherosclerosis independent of preexisting apo B-100 peptide autoantibodies and without an increase in peptide-specific IgG, suggesting that it was mediated by cellular immune responses.

Following the discovery of immunity to HSP 60/65 (127), nasal administration of mycobacterial HSP 65 to LDL receptor-deficient mice maintained on a high-cholesterol diet was shown to be associated with a decrease in atherosclerotic plaque size and macrophage and T-cell numbers in the aortic arch, with an increase in colocalized interleukin-10 expression. A similar trend was observed in orally treated mice (128).

Inhibition of cholesterol ester transfer protein (CETP) prevents the transfer of cholesterol ester from high-density lipoprotein (HDL) to triglyceride-rich lipoproteins in exchange for triglyceride, thereby raising the level of HDL, which is protective against atherosclerosis. In a phase I human trial (129), 8 of 15 subjects (53%) who received two injections of CETP vaccine (which reduced atherosclerosis in rabbits) developed anti-CETP antibodies. Short-term adverse effects were absent, but no follow-up studies have been reported. Recently, intranasal plasmid encoding CETP coupled to chitosan nanoparticles was shown to induce anti-CETP antibodies and significantly reduce atherosclerosis in cholesterol-fed rabbits (130). These cited examples of proof-of-concept for vaccination-induced protection against atherosclerosis in animal models are a strong foundation for human trials. The landscape of emerging vaccines for human atherosclerosis has recently been surveyed (131).

EPILOGUE

The close of the last millennium was the golden age of vaccination for prevention of infectious diseases, despite remaining challenges in specific cases such as malaria and HIV. As we advance into the new millennium, vaccination both in concept and practice is no longer bounded by notions of