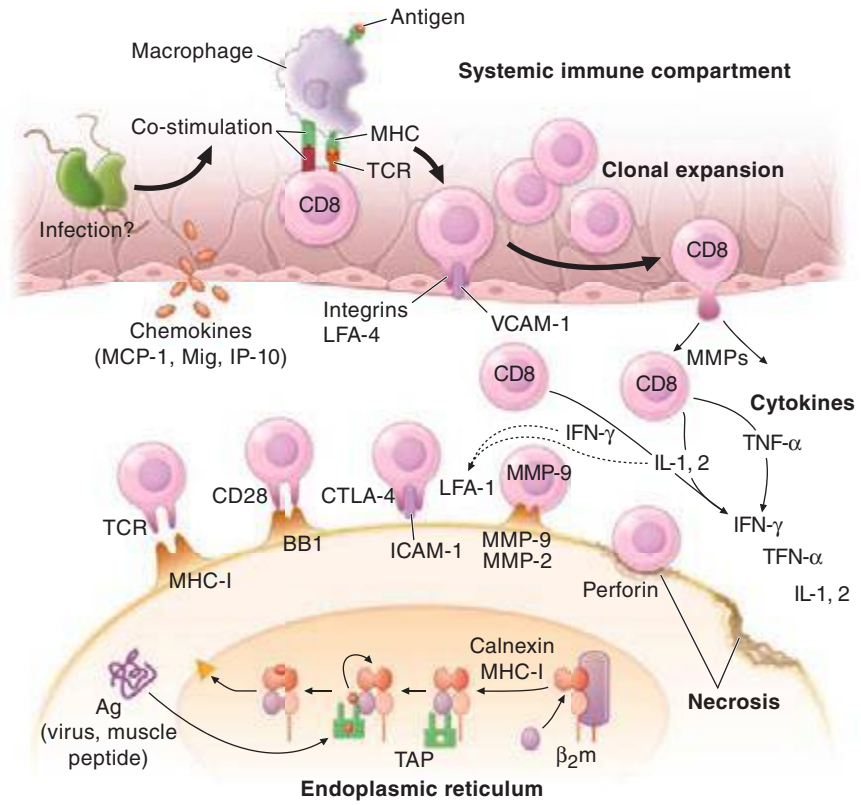

FIGURE 388-2 Cell-mediated mechanisms of muscle damage in polymyositis (PM) and inclusion body myositis (IBM). Antigen-specific CD8 cells are expanded in the periphery, cross the endothelial barrier, and bind directly to muscle fibers via T cell receptor (TCR) molecules that recognize aberrantly expressed major histocompatibility complex (MHC)-I. Engagement of co-stimulatory molecules (BB1 and ICOSL) with their ligands (CD28, CTLA-4, and ICOS), along with ICAM-1/LFA-1, stabilize the CD8–muscle fiber interaction. Metalloproteinases (MMPs) facilitate the migration of T cells and their attachment to the muscle surface. Muscle fiber necrosis occurs via perforin granules released by the autoaggressive T cells. A direct myocytotoxic effect exerted by the cytokines interferon (IFN) γ, interleukin (IL) 1, or tumor necrosis factor (TNF) α may also play a role. Death of the muscle fiber is mediated by necrosis. MHC class I molecules consist of a heavy chain and a light chain (β_2 microglobulin [β_2m]) complexed with an antigenic peptide that is transported into the endoplasmic reticulum by TAP proteins **(Chap. 373e)**.

the dystrophinopathies where inflammatory cell infiltration is often found early in the disease. Such doubtful cases should always be given an adequate trial of glucocorticoid therapy and undergo genetic testing to exclude muscular dystrophy. Identification of the MHC/CD8 lesion by muscle biopsy is helpful to identify cases of PM. Some metabolic myopathies, including glycogen storage disease due to myophosphorylase or acid maltase deficiency, lipid storage myopathies due to carnitine deficiency, and mitochondrial diseases produce weakness that is often associated with other characteristic clinical signs; diagnosis rests upon histochemical and biochemical studies of the muscle biopsy. The endocrine myopathies such as those due to hypercorticosteroidism, hyper- and hypothyroidism, and hyper- and hypoparathyroidism require the appropriate laboratory investigations for diagnosis. Muscle wasting in patients with an underlying neoplasm may be due to disuse, cachexia, or rarely a paraneoplastic neuromyopathy **(Chap. 122)**.

Diseases of the neuromuscular junction, including myasthenia gravis or the Lambert-Eaton myasthenic syndrome, cause fatiguing weakness that also affects ocular and other cranial muscles **(Chap. 461)**. Repetitive nerve stimulation and single-fiber EMG studies aid in diagnosis.

Acute Muscle Weakness This may be caused by an acute neuropathy such as Guillain-Barré syndrome **(Chap. 460)**, transverse myelitis **(Chap. 456)**, a neurotoxin **(Chap. 462e)**, or a neurotropic viral infection such as poliomyelitis or West Nile virus **(Chap. 164)**. When acute weakness is associated with very high levels of serum CK (often in the thousands), painful muscle cramps, rhabdomyolysis, and myoglobinuria, it may be due to a necrotizing autoimmune myositis, as discussed below, a viral infection or a metabolic disorder such as myophosphorylase deficiency, or carnitine palmitoyltransferase deficiency **(Chap. 462e)**. Several animal parasites, including protozoa (*Toxoplasma*, *Trypanosoma*), cestodes (cysticerci), and nematodes (trichinae), may produce a focal or diffuse inflammatory myopathy known as *parasitic polymyositis*. *Staphylococcus aureus*, *Yersinia*, *Streptococcus*, or anaerobic bacteria may produce a suppurative myositis, known as *tropical polymyositis*, or *pyomyositis*. Pyomyositis, previously rare in the west, is now occasionally seen in AIDS patients. Other bacteria, such as *Borrelia burgdorferi* (Lyme disease) and *Legionella pneumophila* (Legionnaire's disease), may infrequently cause myositis.

Patients with periodic paralysis experience recurrent episodes of acute muscle weakness without pain, always beginning in childhood. Chronic alcoholics may develop painful myopathy with myoglobinuria after a bout of heavy drinking. Acute painless muscle weakness with myoglobinuria may occur with prolonged hypokalemia, or hypophosphatemia and hypomagnesemia, usually in chronic alcoholics or in patients on nasogastric suction receiving parenteral hyperalimentation.

Myofasciitis This distinctive inflammatory disorder affecting muscle and fascia presents as diffuse myalgias, skin induration, fatigue, and mild muscle weakness; mild elevations of serum CK are usually present. The most common form is eosinophilic myofasciitis characterized by peripheral blood eosinophilia and eosinophilic infiltrates in the endomysial tissue. In some patients, the eosinophilic myositis/fasciitis occurs in the context of parasitic infections, vasculitis, mixed connective tissue disease, hypereosinophilic syndrome, or toxic exposures (e.g., toxic oil syndrome, contaminated L-tryptophan) or with mutations in the calpain gene. A distinct subset of myofasciitis is characterized by pronounced infiltration of the connective tissue around the muscle by sheets of periodic acid–Schiff-positive macrophages and occasional CD8 T cells (macrophagic myofasciitis or inflammatory myositis with abundant macrophages [IMAM]). A focal form of this disorder, limited to sites of previous vaccinations, administered months or years earlier, has been linked to an aluminum-containing substrate in vaccines. This disorder, which to date has not been observed outside of France, responds to glucocorticoid therapy, and the overall prognosis seems favorable.

Necrotizing Autoimmune Myositis This is an increasingly recognized entity that has distinct features, even though it is often labeled as PM. It presents as an acute or subacute onset of symmetric muscle weakness; CK is typically extremely high. The weakness can be severe. Coexisting interstitial lung disease and cardiomyopathy may be present. The disorder may develop after a viral infection, in association with cancer, or in patients taking statins when the myopathy continues to worsen after statin withdrawal. Some patients have antibodies against signal recognition particle (SRP) or against the 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), a 100-kDa protein considered the pharmacologic target of statins. The muscle biopsy demonstrates necrotic fibers infiltrated by macrophages but only rare, if any, T cell infiltrates. Muscle MHC-I expression is only slightly and focally upregulated. The capillaries may be swollen with hyalinization, thickening of the capillary wall, and deposition of complement. Most patients respond to immunotherapy, but some are resistant.