Vascular Smooth-Muscle Cell The vascular smooth-muscle cell, the major cell type of the media layer of blood vessels, also contributes actively to vascular pathobiology. Contraction and relaxation of smooth-muscle cells at the level of the muscular arteries controls blood pressure and, hence, regional blood flow and the afterload experienced by the left ventricle (see below). The vasomotor tone of veins, which is governed by smooth-muscle cell tone, regulates the capacitance of the venous tree and influences the preload experienced by both ventricles. Smooth-muscle cells in the adult vessel seldom replicate in the absence of arterial injury or inflammatory activation. Proliferation and migration of arterial smooth-muscle cells, associated with functional modulation characterized by lower content of contractile proteins and greater production of extracellular matrix macromolecules, can contribute to the development of arterial stenoses in atherosclerosis, arteriolar remodeling that can sustain and propagate hypertension, and the hyperplastic response of arteries injured by percutaneous intervention. In the pulmonary circulation, smooth-muscle migration and proliferation contribute decisively to the pulmonary vascular disease that gradually occurs in response to sustained high-flow states such as left-to-right shunts. Such pulmonary vascular disease provides a major obstacle to the management of many patients with adult congenital heart disease. Among other mediators, microRNAs have emerged as powerful regulators of this transition, offering new targets for intervention.

Smooth-muscle cells secrete the bulk of vascular extracellular matrix. Excessive production of collagen and glycosaminoglycans contributes to the remodeling and altered functions and biomechanics of arteries affected by hypertension or atherosclerosis. In larger elastic arteries, the elastin synthesized by smooth-muscle cells serves to maintain not only normal arterial structure, but also hemodynamic function. The ability of the larger arteries, such as the aorta, to store the kinetic energy of systole promotes tissue perfusion during diastole. Arterial stiffness associated with aging or disease, as manifested by a widening pulse pressure, increases left ventricular afterload and portends a poor outcome.

Like endothelial cells, vascular smooth-muscle cells do not merely respond to vasomotor or inflammatory stimuli elaborated by other cell types but can themselves serve as a source of such stimuli. For example, when exposed to bacterial endotoxin or other proinflammatory stimuli, smooth-muscle cells can elaborate cytokines and other inflammatory mediators. Like endothelial cells, upon inflammatory activation, arterial smooth-muscle cells can produce prothrombotic mediators such as tissue factor, the antifibrinolytic protein PAI-1, and other molecules that modulate thrombosis and fibrinolysis. Smooth-muscle cells also elaborate autocrine growth factors that can amplify hyperplastic responses to arterial injury.

Vascular Smooth-Muscle Cell Function Vascular smooth-muscle cells govern vessel tone. Those cells contract when stimulated by a rise in intracellular calcium concentration by calcium influx through the plasma membrane and by calcium release from intracellular stores (Fig. 265e-3). In vascular smooth-muscle cells, voltage-dependent L-type calcium channels open with membrane depolarization, which is regulated by energy-dependent ion pumps such as the Na^+,K^+-ATPase pump and ion channels such as the Ca^{2+}-sensitive K^+ channel. Local changes in intracellular calcium concentration, termed *calcium sparks*, result from the influx of calcium through the voltage-dependent calcium channel and are caused by the coordinated activation of a

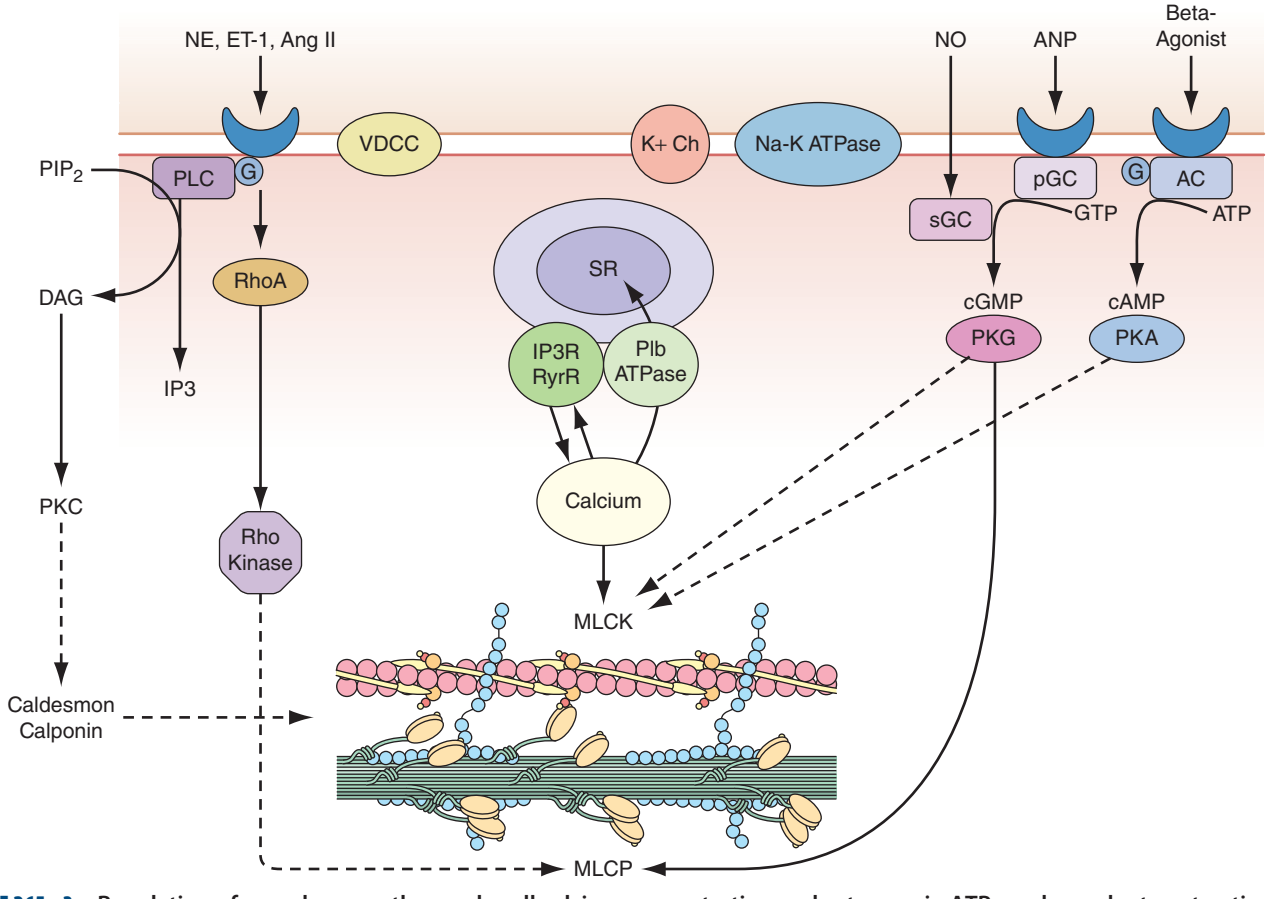

FIGURE 265e-3 Regulation of vascular smooth-muscle cell calcium concentration and actomyosin ATPase-dependent contraction. AC, adenylyl cyclase; Ang II, angiotensin II; ANP, atrial natriuretic peptide; DAG, diacylglycerol; ET-1, endothelin-1; G, G protein; IP_3, inositol 1,4,5-trisphosphate; MLCK, myosin light chain kinase; MLCP, myosin light chain phosphatase; NE, norepinephrine; NO, nitric oxide; pGC, particular guanylyl cyclase; PIP_2, phosphatidylinositol 4,5-bisphosphate; PKA, protein kinase A; PKC, protein kinase C; PKG, protein kinase G; PLC, phospholipase C; sGC, soluble guanylyl cyclase; SR, sarcoplasmic reticulum; VDCC, voltage-dependent calcium channel. *(Modified from B Berk, in Vascular Medicine, 3rd ed. Philadelphia, Saunders, Elsevier, 2006, p. 23; with permission.)*