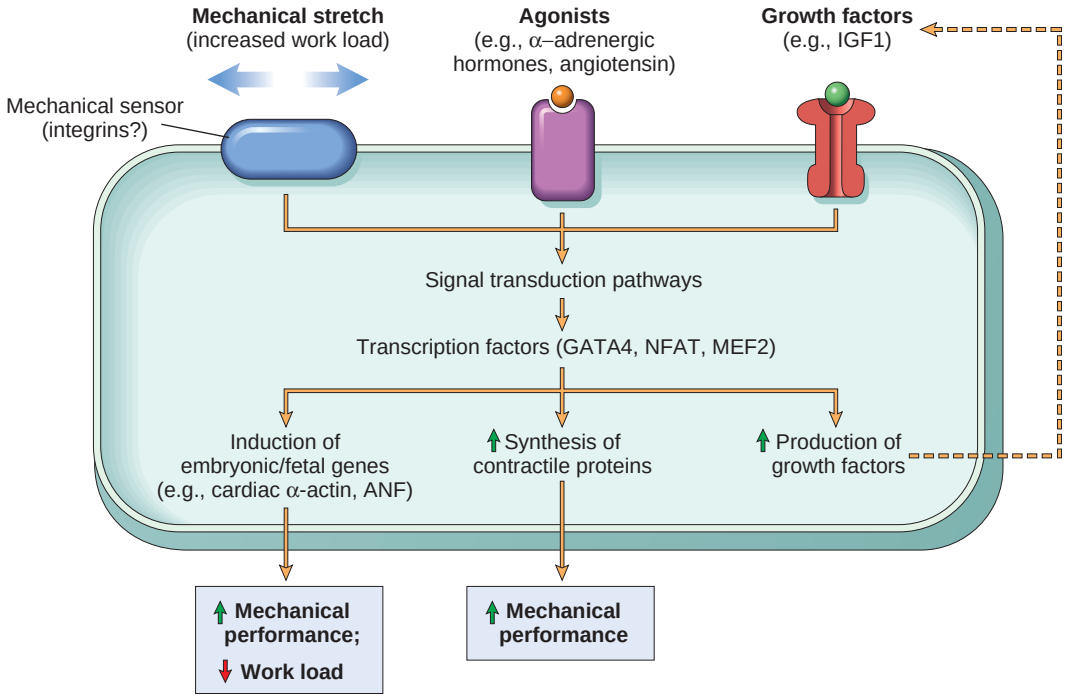

Figure 2-4 Biochemical mechanisms of myocardial hypertrophy. The major known signaling pathways and their functional effects are shown. Mechanical sensors appear to be the major triggers for physiologic hypertrophy, and agonists and growth factors may be more important in pathologic states. ANF, Atrial natriuretic factor; GATA4, transcription factor that binds to DNA sequence GATA; IGF1, insulin-like growth factor; NFAT, nuclear factor activated T cells; MEF2, myocardial enhancing factor 2.

sudden death (Chapter 11). There are three basic steps in the molecular pathogenesis of cardiac hypertrophy:

- The integrated actions of mechanical sensors (that are triggered by increased workload), growth factors (including TGF-β, insulin-like growth factor 1 [IGF1], fibroblast growth factor), and vasoactive agents (e.g., α-adrenergic agonists, endothelin-1, and angiotensin II). Indeed, mechanical sensors themselves induce production of growth factors and agonists (Fig. 2-4).
- These signals originating in the cell membrane activate a complex web of signal transduction pathways. Two such biochemical pathways involved in muscle hypertrophy are the phosphoinositide 3-kinase (PI3K)/AKT pathway (postulated to be most important in physiologic, e.g., exercise-induced, hypertrophy) and signaling downstream of G-protein–coupled receptors (induced by many growth factors and vasoactive agents, and thought to be more important in pathologic hypertrophy).
- These signaling pathways activate a set of transcription factors such as GATA4, nuclear factor of activated T cells (NFAT), and myocyte enhancer factor 2 (MEF2). These transcription factors work coordinately to increase the synthesis of muscle proteins that are responsible for hypertrophy.

Hypertrophy is also associated with a switch of contractile proteins from adult to fetal or neonatal forms. For example, during muscle hypertrophy, the α isoform of myosin heavy chain is replaced by the β isoform, which has a slower, more energetically economical contraction. In addition, some genes that are expressed only during early development are reexpressed in hypertrophic cells, and the products of these genes participate in the cellular response to stress. For example, the gene for atrial natriuretic factor is expressed in both the atrium and the ventricle in the embryonic heart, but it is down-regulated after birth. Cardiac hypertrophy is associated with increased atrial natriuretic factor gene expression. Atrial natriuretic factor is a peptide hormone that causes salt secretion by the kidney, decreases blood volume and pressure, and therefore serves to reduce hemodynamic load.

Whatever the exact cause and mechanism of cardiac hypertrophy, it eventually reaches a limit beyond which enlargement of muscle mass is no longer able to cope with the increased burden. At this stage several regressive changes occur in the myocardial fibers, of which the most important are lysis and loss of myofibrillar contractile elements. In extreme cases myocyte death can occur. The net result of these changes is cardiac failure, a sequence of events that illustrates how an adaptation to stress can progress to functionally significant cell injury if the stress is not relieved.

To prevent such consequences, several drugs that inhibit key signaling pathways involving *NFAT, GATA4,* and *MEF2* genes are in phase 1 or 2 clinical trials.

Hyperplasia

Hyperplasia is defined as an increase in the number of cells in an organ or tissue in response to a stimulus. Although hyperplasia and hypertrophy are distinct processes, they frequently occur together, and may be triggered by the same external stimulus. Hyperplasia can only