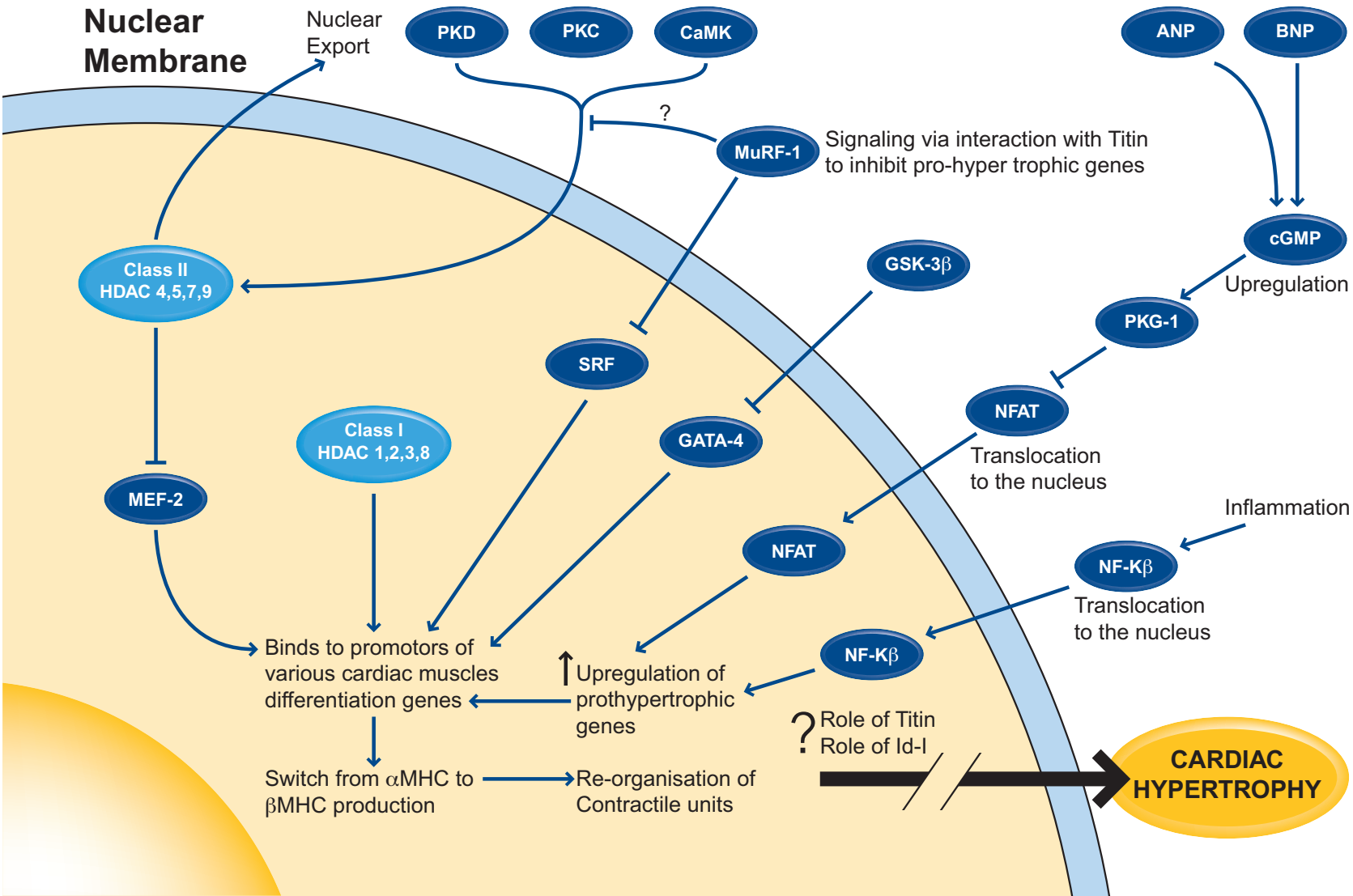
The Hypertrophy pathway



The hypertrophic pathway is associated with either up-regulation, or loss of inhibition of Pro-hypertrophic proteins or down-regulation of anti-hypertrophic proteins.

Pro-hypertrophic Response

PKD & PKC phosphorylate Class II HDACs resulting in the nuclear export of these proteins.
Up regulation of MEF2, SRF (possibly via loss of inhibition by MuRF-1), GATA-4 (Via loss of inhibition by GSK-3β), can lead to these factors binding to the promoters of various cardiac muscle differentiation genes leading to a switch in gene expression e.g. a switch from α-MHC production to β-MHC production, this in turn leads to a increase in the sarcomeric numbers and a re-organisation of the conractile units leading to the cardiac hypertrophy phenotype.
Inflammation can result in translocation of NF-kB to the nucleus where this protein can lead to up-regulation of pro-hypertrophic genes, in a similar way, translocation of NFAT to the nucleus, via loss of PKG-1 inhibition also has an affect on the expression of pro-hypertrophic genes.

Anti-hypertrophic response

The anti-hypertrophoc response is mainly mediated through inhibition of the main proteins, so that, HDAC Class II proteins, if localised to the nucleus function by inhibiting the action of MEF-2. MuRF-1 has been shown to inhibit the function of SRF, in a similar manner, GSK-3β has been shown to inhibit the function of GATA-4.

What is less understood is the role of anti-hypertrophy genes e.g. Titin and Id-1. These proteins do not appear to be anti-hypertrophic factors because they inhibit other proteins, but instead they actively promote anti-hypertrophy.

Class II HDACs are known for their anti-hypertrophic properties. These possibly mediate their effects through interaction and inhibition of MEF2. It has been suggested that PKC and PKD can phosphorylate class II HDACs leading to their export from the nucleus resulting in a pro-hypertrophic phenotype.