An orphan GPCR finds a home in the heart

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G PROTEIN-COUPLED RECEPTORS (GPCRs) are the largest and most successful targets for pharmacotherapy to date, particularly in the area of cardiovascular disease. These receptors are at the forefront of current drug discovery efforts (7). GPCRs also form the largest family of transmembrane receptors, with nearly 800 GPCR loci (12, 18), of which several hundred are categorized as orphan GPCRs. These orphan receptors have no known endogenous ligand. While it is estimated that 300 or so of these genes are olfactory or chemosensory receptors, ~100 or more GPCR orphans remain that may have putative hormonal or neurotransmitter-related functions (3) providing novel targets for disease. Thus, orphans have attracted significant attention in recent years to determine their expression profiles and roles, if any, in physiology and disease.

Orphan GPCR research has progressed rapidly in recent years. Originally, researchers used reverse pharmacology by using orphan GPCRs as “hooks” in screening to fish out novel hormone, peptide, and neurotransmitter ligands. This approach has identified novel neuropeptides that regulate feeding, satiety, circadian rhythms, and sleep (3, 17). More recently, large compound libraries have been used to identify chemicals that interact with orphan GPCRs that may have therapeutic potential (4). In all, these efforts have “deorphanized” more than 40 GPCRs, and many of these targets are the focus of ongoing drug development efforts in academia and industry (3, 7).

In this issue, a report by Adams et al. (1) makes headway in orphan receptor research. These investigators report not the deorphanization, in a strict sense, of an orphan GPCR but instead detail the signaling and likely physiological role of GPR22 in the heart. Adams et al. (1) show that GPR22 is expressed at high levels in cardiac tissue and that this receptor has constitutive activity, signaling through Goq activation, and inhibition of cAMP production. Furthermore, the data indicate that GPR22 mRNA levels were reduced in mice subjected to transverse aortic constriction (TAC), a pressure overload model of cardiac hypertrophy. This finding led Adams and colleagues to generate GPR22 knockout (GPR22−/−) mice and interrogate the cardiac phenotype. GPR22−/− mice have an increased susceptibility to cardiac hypertrophy and cardiac dysfunction following TAC. Taken together, these findings make a strong case for a physiological role for the orphan receptor, GPR22, in cardiac hypertrophy.

Cardiac hypertrophy is a general term used to describe the growth response of the myocardium to alter its size and geometry. This response is due to stresses that increase demand for energy and comes in two flavors: 1) exercise is associated with physiological growth where there is a uniform increase in the size of the ventricular wall and septum, leading to proportional changes in the chambers and resulting in preserved function, and does not have any associated fibrosis; or 2) a pathological hypertrophy in response to such stresses as myocardial ischemia, pulmonary or systemic arterial hypertension, or valvular heart disease, where growth is nonuniform (a greater increase in myocyte width than length) and leading to disproportional chamber growth, which initially can be compensatory but ultimately becomes detrimental with extensive fibrosis, myocyte death, and cardiac dysfunction (10, 14). Interestingly, Adams et al. (1) describe two pieces of data (i.e., expression of GRP22 is reduced in wild-type animals undergoing TAC and TAC in GPR22−/− mice results in impaired cardiac function and signs of chamber dilation) that suggest a role for GRP22 in either limiting pathological hypertrophy or possibly promoting physiological hypertrophy.

The signaling scheme involved in cardiac hypertrophy is complex. Pathological hypertrophy is thought to involve the activation of GPCRs coupled to Goq (2, 11, 16), downstream activation of phospholipase C (5), and subsequent divergent pathways through PKC and MAPKs or calcium, calcineurin, and nuclear factor of activated T cells leading to hypertrophy (10, 14). Physiological hypertrophy involves growth factors that activate receptor tyrosine kinases coupled to phosphoinositide 3-kinase (PI3K) and protein kinase B (Akt) to affect mammalian target of rapamycin (mTOR) to impact physiological growth (14).

Although insulin-like growth factor 1 has been predominantly implicated in initiating signaling leading to physiological hypertrophy, there is clear evidence in the literature that Gq-coupled GPCRs are able to activate PI3K, Akt, and mTOR mainly in the setting of myocardial ischemia-reperfusion injury (8, 9). The observation in the present report (1) that GRP22 is coupled to Gq and may be linked to protective signaling suggests that there may exist cross-talk that permits such secondary signaling to feed into physiological hypertrophy. There is also clear evidence that Gq-linked pathways are prosurvival and that this protective signaling involves the activation of PKC and MAPK as well as PI3K and Akt (6). The role such dual activation may play on the final outcome of physiological versus pathological hypertrophy is debatable and should be the modus operandi of future investigations.

The findings presented in the present report (1) must be considered in light of certain limitations that do not necessarily detract from the present study but provide fodder for future investigations. Although there is evidence presented that GPR22 is Gq, coupled, no evidence is presented to suggest what downstream kinases are activated. With respect to protection there are only limited data on a hypertrophic phenotype reflected by diminished cardiac function as assessed by echocardiography. The impact of GPR22 on cardiac myocyte apoptosis and cell size and cardiac fibrosis would be necessary to further expand upon the role of GPR22 in hypertrophic patho-
physiology. Additionally, the result of a null phenotype in unstimmed GRP22−/− mice suggests a compensated phenotype. The development of adenoviral vectors to overexpress or knockdown GRP22 in wild-type hearts, as well as the generation of GRP22 transgenic mice, will be necessary to truly define a protective role of GRP22 in a stressed, hypertrophied heart. The dissection of these limitations will be important in defining a clear place of GRP22 in myocardial function.

Limitations aside, this report by Adams et al. (1) leaves readers with many intriguing questions. Most obvious of these is whether GPR22 has an endogenous ligand. If so, could such an endogenous entity confer the constitutive activity observed in this report? The authors were careful to measure GPR22 receptor activity in cultured cells outside the presence of serum, likely eliminating the possibility that an unknown ligand was present to activate the receptor. However, the cells themselves could produce this unknown factor, resulting in the observed constitutive activity. Other GPCRs that possess detectable constitutive activity have been found to form dimers (15). Does GPR22 form dimers or other types of cooperative signaling complexes that are central to the physiological role of the receptor? Is the level of constitutive activity of GPR22 observed in the cell studies by Adams et al. (1) sufficient to yield the significant physiological effect observed in knockout mice? If not, an alternative hypothesis is that GPR22 dimerizes with another GPCR and alters its function. The loss of one partner in a GPCR heterodimer, as in the case of GPR22 knockout mice, could alter another receptor’s pharmacology, signaling, internalization, or desensitization (13). Further investigation into the molecular partners and subcellular localization of GPR22 and the global signaling events associated with this receptor may provide answers regarding its activation mechanism.

Thus, while GPR22 is still an orphan since it has no identifiable ligand, it does seem to have found a temporary home in the heart; the permanence of this remains to be seen. This report opens our eyes to a new and exciting therapeutic target in the myocardium as well as ushers in a new dynamic in orphan GPCR research by defining a phenotype of an orphan receptor without deorphanizing it. It is said that an orphan has a future but no past, an adage that seems apropos for GPR22.

REFERENCES
