exploited. For example, it will be necessary to develop better means to identify these cells with specific markers; to improve understanding of the mechanisms that induce these cells, either naturally or during therapy; to enhance understanding of the mechanism(s) of suppression; and to improve insight into the signaling events that underlie the selective induction of Hsp60 in intermediate-avidity CD4+ T cells. It will also be important to better define the role of CD94/NKG2A, the receptor on NK cells and a subset of CD8+ T cells that is inhibited by Qa-1/Qdm or HLA-E/B7sp complexes (20), in conferring self/nonself tolerance. Other outstanding questions are whether Qa-1/HLA-E–restricted CD8+ Tregs represent a separate lineage of T lymphocytes and whether HLA-E polymorphisms are associated with human disease, as has been suggested for T1D (24). Finally, it will be important to determine how these cells impact immune responses during different immunological situations such as infection, allograft rejection, cancer, and allergies. With more studies like those performed by Jiang and colleagues (5), answers to many of these questions should be within reach, bringing us closer to attaining the holy grail of immunology.

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Location, location, location, regulation: a novel role for β-spectrin in the heart

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Voltage-gated Na+ channels (VGSCs) are responsible for the rising phase of the action potential in excitable cells, including neurons and skeletal and cardiac myocytes. Small alterations in gating properties can lead to severe changes in cellular excitability, as evidenced by the plethora of heritable conditions attributed to mutations in VGSCs highlighting the need to better understand VGSC regulation. In this issue of the JCI, Hund et al. identify the ability of a key structural protein, βν-spectrin, to bind and recruit Ca2+/calmodulin kinase II to the channel at a cellular location key to successful action potential initiation and propagation, where it can mediate function and excitability.

The Na+ channel and disease
In excitable tissues, such as muscle, heart, and nerve, action potential (AP) initiation is most often accomplished by the opening of voltage-gated Na+ channels (VGSCs). VGSC activity is critical for normal impulse conduction and contributes to control of the duration and morphology of the cellular AP. VGSCs have a primary pore-forming α subunit that is a protein with 4 homologous domains, each with 6 transmembrane segments (Figure 1).

Inward Na+ current is typically the largest membrane current in excitable cells and must quickly inactivate to allow the cell to begin to repolarize. In myocytes, NaL.5 (which is encoded by SCNSA) is the principal VGSC α subunit expressed. It is predominantly localized in the inter-
When VGSCs fail to inactivate normally, the AP, lead to long QT syndrome (2). Late Na+ current is linked to Na+ channel as a CaMKII binding protein that participates in the Na+,Ca2+ macromolecular complex in cardiac myocyte intercalated discs (ref. 19 and Figure 2B). Therefore, βn-spectrin appears analogous to the more ubiquitous AKAPs in that it recruits a kinase to a local signaling environment involving an ion channel. Moreover, Hund et al. found that βn-spectrin was required for the action of CaMKII on Na+,1.5 (19). In mouse cardiomyocytes, abolishing CaMKII activity via a mutation in βn-spectrin positively shifted baseline Na+ channel steady-state inactivation (SSI) and eliminated the late Na+ current and SSI shift normally induced by β-adrenergic receptor stimulation by isoproterenol. Hund and colleagues further demonstrated that this was caused by βn-spectrin directly regulating CaMKII-mediated phosphorylation of a specific serine residue in the Na+,1.5 I–II linker, S571. Consistent with the present understanding of the functional role of Na+ channel activity in the heart, the hyperpolarizing shift in SSI observed in mice expressing mutant forms of βn-spectrin led to reduced excitability, and the decrease in late current resulted in shortened APD and a subsequent decrease in Na+ channel activity.}

**Figure 1**
The α subunit of the cardiac Na+ channel. DI–DIV denotes the 4 homologous domains of the α subunit; S1–S6 denote the 6 transmembrane segments. S5 and S6 are the pore-lining segments, and the S4 helices (black) serve as voltage sensors. In the connecting loop between DIII and DIV, the 3 residues isoleucine, phenylalanine, and methionine (IFM) are known to play a key role in the fast inactivation process.
in QT interval. The finding of Hund et al. that βIV-spectrin associated with CaMKII in cerebellar Purkinje neurons targeting it to the axonal initial segments — critical regions for the generation of APs in which VGSCs localize — suggests that the key modulatory roles of βIV-spectrin may very well exist in the brain, and perhaps other tissues, in addition to the heart.

Conclusions and perspective
There has been increasing understanding that ion channels do not exist on cell membranes simply as pore-forming proteins, but are instead in complex with a host of proteins that can influence the channel in a multitude of ways, including aiding channel targeting to specific subcellular regions, controlling the phosphorylation state of the channel, participating in biosynthesis and degradation of the channel, and altering channel gating allosterically. The present study by Hund et al. increases our understanding of the molecular identity of the complex controlling the phosphorylation state of the predominant cardiac VGSC (19). As phosphorylation of the channel affects channel-gating properties (i.e., SSI and late Na⁺ current), and small perturbations in these properties are linked to disease in a number of systems, understanding the molecular components in this pathway represents a significant contribution to the field. Subsequently, this molecular pathway may represent a novel therapeutic target or serve as a new locus for heritable channelopathies. Furthermore, the ability of βIV-spectrin to recruit CaMKII to distinct subcellular compartments critical to cellular excitability in other cell types may indicate a broader role within the cell, as it can serve not only as a structural protein, but also in the regulation of posttranslational states of membrane proteins.

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Obesity is associated with infiltration of white adipose tissue (WAT) by macrophages, which contributes to the development of insulin resistance. In this issue of the JCI, Kosteli and colleagues demonstrate that weight loss is unexpectedly also associated with rapid, albeit transient, recruitment of macrophages to WAT and that this appears to be related to lipolysis.

Macrophages are derived from monocytes and comprise a heterogenous population of cells found in nearly all tissues (1). In addition to their pivotal role in host defense, inflammation, and tissue repair, studies over the last decade have focused on their role in chronic metabolic diseases, such as obesity and insulin resistance (2). The initial descriptions of macrophage infiltration of white adipose tissue (WAT) during obesity, which were published in the JCI in 2003 (3, 4), garnered a great deal of attention, as evidenced by over 1,000 subsequent reports that confirmed the link between adipose tissue macrophages (ATMs) and inflammation and insulin resistance. In contrast, the role of innate and adaptive immunity in weight loss, the ultimate translational goal of research on obesity, is less clear. In this issue of the JCI, Kosteli and colleagues report that acute weight loss results in recruitment of macrophages to WAT (5). However, in this case, the recruited macrophages do not promote inflammation but rather regulate lipolysis. Since stimuli that enhance adipocyte lipolysis increase macrophage recruitment to WAT, the authors suggest that release of FFAs is a general signal for macrophage recruitment.

Obesity, inflammation, and macrophages

The chronic, low-grade inflammation that is characteristic of obesity has long been suspected to contribute to the development of insulin resistance (6). Almost two decades ago, Spiegelman and colleagues demonstrated that TNF-α, which is induced in the adipose tissue of obese animals, inhibits glucose disposal by promoting insulin resistance in peripheral tissues (7). Although adipocytes were identified as the source of TNF-α, expression of TNF-α was also observed in the stromalvascular fraction rich in immune cells. This observation fueled a new direction in metabolic research and led to the discovery that macrophage infiltration of WAT is responsible for obesity-associated inflammation (3, 4). While WAT from lean animals contains a resident population of alternatively activated macrophages (also known as M2 macrophages), which are characterized by expression of F4/80, CD206, and arginase 1 (Arg1), obesity is associated with recruitment of classically activated macrophages complex is essential for membrane excitability in mice. J Clin Invest. 2010;120(10):3508–3519.

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In obesity and weight loss, all roads lead to the mighty macrophage

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