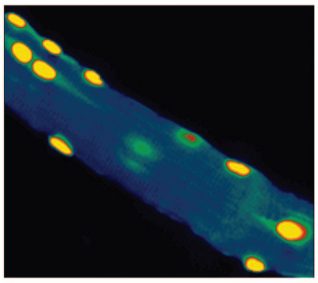
In this ISSUE

Calcium Levels in a SNAP

Signaling through calcium ions is critical for numerous cellular processes. Cells have devised intricate mechanisms for managing Ca^{2+} function, including retaining precise control over spatial and temporal Ca^{2+} levels. However, our capacity to investigate these mechanisms has been hampered by a lack of tools that enable the simultaneous monitoring of Ca^{2+} concentrations at a precise location and a given time. Bannwarth *et al.* (DOI 10.1021/cb800258g) and Point of View (DOI 10.1021/cb9000525) elegantly combine SNAP-tag fusion protein technology with synthetic calcium indicators to generate a method for examining the spatial and temporal regulation of Ca^{2+} levels in cells.

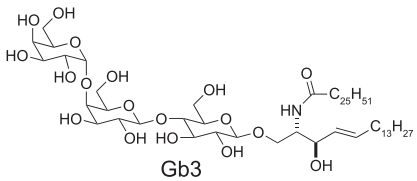
SNAP-tag fusion proteins comprise an engineered human O^6-alkylguanine-DNA alkyltransferase (AGT) that reacts specifically with O^6-benzylguanine (BG) derivatives. Ca^{2+}-Sensitive SNAP-tag fusion proteins were created by synthesizing a BG derivative containing the Ca^{2+} indicator Indo-1. To evaluate the utility of the Ca^{2+}-sensitive SNAP-tag fusion in cells, a SNAP-tag fusion containing a nuclear localization sequence was created, and local Ca^{2+} levels were monitored in cultured primary muscle cells.



A Sweet Killer Instinct

Natural killer T (NKT) cells did not get their name for nothing. They are programmed to recognize and destroy foreign cells such as those from viruses and tumors. T cell receptors on NKT cells recognize glycolipids presented by target cells, which triggers a signaling cascade culminating in the launch of an appropriate immune response. In most of the glycolipids recognized by NKT cells, such as α-galactosylceramides, α-glycosylceramides, and α-glycosyldiacylglycerols, an alpha linkage connects the carbohydrate moiety to the lipid group, and lysosomal processing to a single carbohydrate unit is required for NKT cell stimulation. However, the triglycosylceramide iGb3 appears to reject both of these requirements, as a beta linkage connects a trisaccharide to the ceramide unit, yet this glycolipid also stimulates NKT cells. Now, Yin *et al.* (DOI 10.1021/cb800277n) explore the structural features of iGb3 derivatives to further characterize the requirements for NKT cell activation.

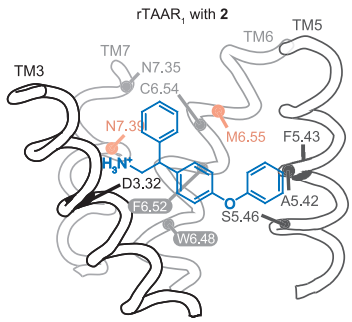
Synthesis of the alpha anomers of iGb3 and the related, nonstimulatory Gb3 glycolipid was followed by evaluation of the compounds as NKT cell stimulants. Intriguingly, both alpha-configured glycolipids were capable of activating NKT cells, implicating triglycosylceramides as a new class of NKT cell antigens.



Tracing Species Specificity

The trace amine-associated receptor 1 ($TAAR_1$) is a G protein-coupled receptor activated by derivatives of thyroid hormone including 3-iodothyronamine and tyramine. The biological role of members of the TAAR family is not clearly defined, but their activation by thyroid hormone derivatives as well as psychostimulants such as amphetamine implicate them as potential players in numerous important physiological processes. Surprisingly, despite 93% sequence similarity between rat and mouse $TAAR_1$, structure–activity studies with 3-iodothyronamine analogs have revealed that the receptors exhibit distinct ligand-binding preferences. Now, Tan *et al.* (DOI 10.1021/cb800304d) explore the origin of this intriguing species-specific difference in $TAAR_1$ receptors.

Evaluation of the binding of various 3-iodothyronamine analogs with single and double mutants of rat and mouse $TAAR_1$ indicated that key residues in two transmembrane helices within the ligand binding site house the molecular basis for the ligand specificity. These findings will facilitate further characterization of the structural determinants involved in the species-specific binding properties of $TAAR_1$ receptors, offering clues into the role of the human $TAAR_1$ receptors as well.



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