'Calcium-Sensing Receptor' Review Series **Review series on the extracellular Ca^{2+} -Sensing Receptor****Aldebaran M. Hofer ****Guest Editor*

Faithful control of systemic Ca^{2+} homeostasis is crucial for life for most, if not all, multi-cellular organisms. In humans and many other vertebrates, extracellular Ca^{2+} is detected by a specific G-protein coupled receptor (GPCR) for divalent cations, the extracellular Ca^{2+} -sensing receptor (CaR) [1]. With this issue, I am pleased to launch a new review series in the *Journal of Cellular and Molecular Medicine* on this fascinating receptor.

The idea that a sensor for extracellular divalent cations existed in mammals was not entirely new. It was apparent from early studies throughout the 1980s that some type of cell-surface receptor coupled to intracellular signal transduction cascades must be present on the parathyroid gland in order to account for the ability of this endocrine organ to sense and respond to minute fluctuations in circulating Ca^{2+} levels [1–3]. However, the actual cloning of the CaR from the bovine parathyroid by Brown, Hebert, Riccardi and colleagues in 1993 transformed this field [4], permitting a detailed look into the structure-function relationships of the CaR. This also eventually led to the somewhat surprising conclusion

that the CaR was expressed at varying levels in numerous tissues apart from the parathyroid gland. With the sequence in hand, it also soon became apparent that naturally occurring mutations in CaR accounted for a number of human disorders of systemic Ca^{2+} handling. CaR, in fact, is a rare example of a GPCR for which the numerous mutations identified in humans have been unequivocally linked to disease, ranging from severe (even lethal) endocrine dysfunction to largely benign alterations in mineral homeostasis.

In the first review article appearing in this issue, Huang and Miller explore the ways in which proteins that interact with CaR can influence the function of the receptor. These authors point out that the simple 'linear' model of GPCR signalling in which CaR interacts with heterotrimeric G-proteins in order to modulate second messenger concentrations is difficult to reconcile with the wide variety of biological actions of CaR stimulation observed in different cell types. Huang and Miller suggest that distinct signalling 'personalities' can derive from interactions of CaR with specific interacting proteins. Here, they

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discuss how CaR interacts with inwardly rectifying potassium channels (members of the Kir family), receptor activity modifying proteins (RAMPs), the scaffolding protein filamin and other proteins that form the CaR-based signalling complex.

In the second article of this series, Hu and Spiegel present a comprehensive look at the structure-function relationships of the CaR. Many of these insights have been obtained through examination of the functional attributes of receptors containing natural mutations identified in patients, as well as through engineered mutations. The similarity of CaR with the metabotropic glutamate receptor type 1, for which a partial crystal structure has been solved, allows further predictions as to the structural and functional domains of CaR. Finally, the actions of specific allosteric modulators of the receptor, many of which are now used clinically (or are being developed) to treat a variety of disorders linked to the CaR, have also revealed important insights into the detailed workings of this interesting receptor.

I hope the readers of JCMM will enjoy these two informative articles as much as I have.

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Guest Editor

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