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Sommario/riassunto	The development of the field of membrane guanylate cyclase transduction system has been colorful, filled with exceptional historical events in cellular signaling research. From denial to resurgence, the field has branched in multiple directions. The signal transduction characteristics and signaling elements are unique. The field has established cyclic GMP as an ubiquitous intracellular second messenger, playing a critical role in the control of many physiological processes, including cardiac vasculature, smooth muscle relaxation, blood volume, cellular growth, sensory transduction, neural plasticity, learning and memory. Unlike the three-component design of its predecessor: adenylate cyclase, G-protein and G-protein coupled receptor, the membrane guanylate cyclase transduction system consists of a single entity, a trans-membrane-spanning protein that serves as both a receptor and a signal transducer. Membrane guanylate cyclases exist in multiple forms. Each form translates the captured signal at a structurally conserved core catalytic site that resides in the intracellular domain. Yet the mechanism of capturing the signal is unique to each form. The surface receptor form uses its extracellular domain to

capture hormonal signals; the Ca2+-modulated ROS-GC employs its intracellular domains; and the olfactory receptor ONE-GC captures odorant signals at its extracellular domain and amplifies them at multiple intracellular domains. The composition of the hormone receptor form differs from the ROS-GC and ONE-GC forms, consisting of a single polypeptide, that is both a signal receptor and the transducer. In contrast, both ROS-GC and ONE-GC are multi-component systems. A Ca2+ sensing subunit(s) captures the signal and transmits it to a companion guanylate cyclase, that transduces it. Moreover, the modes of signal transduction vary in ROS-GC and ONE-GC. ROS-GC is a direct transducer of Ca2+ signals but the Ca2+ sensors in ONE-GC only amplify the odorant signal received and transmitted by its extracellular domain. An additional refinement is that ROS-GC1 is a bimodal Ca2+ switch, turned “OFF” as intracellular [Ca2+] rises above 75 nM, but then turned back “ON” when [Ca2+] exceeds 345 nM. These modes occur uniquely in the outer segments and synapses of cones in rodent retinas. In a new paradigm change, the dogma has been shattered that the ANF hormone receptor guanylate cyclase, ANF-RGC, is the specific transducer of ANF alone. It is now known that ANF-RGC also transduces a Ca2+ signal. Ca2+ captured by its sensor neurocalcin (NC) directly activates the catalytic module of ANF-RGC. Accordingly, and impressively, targeted gene-deletion mouse model studies demonstrate that both pathways are linked with blood pressure regulation. Their disruption causes hypertension. Thus the ANF-RGC combines features of hormone receptor and ROS-GC forms of membrane guanylate cyclases. These studies also broaden the classification of the Ca2+ sensors. NC, classified as a neuronal calcium sensor, is more widespread. The general theme of this Research Topic is to present a comprehensive coverage of the expanding role being played by this beautifully designed transduction machinery. The reviews will cover its history to its present status, move on to theoretical and experimental investigations propelling the field in future directions, and provide illustrations where the field contributes to clinical medicine.