Structure and gating mechanisms of ATP activated P2X receptor channels

P2X receptor channels are trimeric ATP-activated cation channels that serve important roles in sensory signaling, pain and inflammation. X-ray structures of these receptors show that the large extracellular domain contains ATP binding sites, and an unanticipated central chamber proposed to serve a regulatory function. Comparison of apo and ATP-bound structures reveals the design of the transmembrane (TM) pore, and provide a foundation for understanding the conformational changes occurring during opening. One remarkable feature of the ATP-bound structure is the presence of large crevices between subunits within the TM domain. I will discuss a series of accessibility and metal bridging studies that explore structural relationships between TM helices in both closed and open states for functional P2X receptors embedded in lipid membranes. I will also discuss how divalent cations regulate the function of P2X receptors, and show evidence for subtype-specific activation of P2X receptors by free and divalent bound ATP, and for a regulatory role of the central chamber in the extracellular domain.

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