(P14) Distinct roles of inositol 1,4,5-trisphosphate receptor type 1 and type 3 in Ca^{2+} signaling as revealed by the RNAi technique

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Three subtypes of inositol 1,4,5-trisphosphate receptor (IP_3R1-3) Ca^{2+}-release channel share basic properties but differ in terms of regulation. To what extent they contribute to complex Ca^{2+} signaling, such as Ca^{2+} oscillations, remains largely unknown. Here we show that HeLa cells express comparable amount of IP_3R1 and IP_3R3 but knockdown by RNA interference of each subtype results in dramatically distinct Ca^{2+} signaling patterns. Knockdown of IP_3R1 significantly decreases whole Ca^{2+} signals and terminates Ca^{2+} oscillations. Conversely, knockdown of IP_3R3 leads to more robust and long-lasting Ca^{2+} oscillations than control. Effect of IP_3R3 knockdown is surprisingly similar in COS-7 cells that predominantly (>90% of total IP_3R) express IP_3R3, suggesting that IP_3R3 functions as anti-Ca^{2+}-oscillatory unit without contributing to peak amplitude of Ca^{2+} signals, irrespective of its relative expression level. We also show that these subtypes differentially contribute to the Ca^{2+} leak process, but are dispensable for its subsequent Ca^{2+} entry. Therefore, differential expression of IP_3R subtype is critical factor for various Ca^{2+} signaling and, particularly, IP_3R1 and IP_3R3 have opposite roles in generation of Ca^{2+} oscillations.