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Functional dissection of the cGK substrate IRAG using transgenic models

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NO/cGMP signalling via cGMP-dependent kinase I (cGKI) induces a variety of physiological functions comprising relaxation of smooth muscle and inhibition of platelet aggregation. Several signalling pathways of cGKI exist including the interaction of the cGKIβ isozyme with the inositol 1,4,5-trisphosphate receptor I (IP_3RI) associated protein cGMP kinase substrate (IRAG). To get insight into the physiological function of IRAG protein a knockout mutant of the IRAG gene was generated by targeted deletion. Expression of other cGKI substrate proteins in mutant smooth muscle tissues and platelets was not affected upon IRAG deletion. Interestingly, the localization of cGKIβ was unchanged in IRAG-deficient vascular smooth muscle cells. Analysis of smooth muscle contractility suggests that signalling via IRAG is essential for endogenous and exogenous NO/cGMP-dependent contractility of aortic smooth muscle. Furthermore, NO/cGMP-dependent relaxation of murine colon is dependent on this signalling cascade. In platelets, IRAG-deficiency abolishes the NO/cGMP-dependent inhibition of platelet aggregation and granule secretion. These results strongly suggest that IRAG signalling is a predominant physiological signalling pathway of NO/cGMP in smooth muscle and platelets.