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Genetic dissection of signaling via cGMP-dependent protein kinases

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Increasing evidence suggests that the second messenger cGMP plays a central role in health and disease, but the downstream mechanisms of cGMP-dependent signaling are not well understood. The cGMP-dependent protein kinase type I (cGKI) is an attractive candidate mediator of cGMP signaling, but the pharmacological analysis of cGKI function is limited by the lack of highly specific cGKI activators and inhibitors. To study the (patho)physiological roles of cGKI in vivo, conventional and conditional cGKI knockout mouse models have been established. Whereas cGKI null mutants have a decreased life span (50% of these mice die before 5 to 6 weeks of age), tissue-specific mutants lacking cGKI selectively in the cerebellum, hippocampus, cardiomyocytes, or smooth muscle cells are fully viable allowing one to perform long-term experiments and to study the cell type-specific role of cGKI in adult animals. The analysis of cGKI-deficient mouse models showed that this protein kinase contributes to many (but not all) effects of cGMP in the cardiovascular, gastrointestinal, and nervous system. For instance, cGKI is involved in the acute regulation of smooth muscle tone and platelet aggregation, but is most likely not essential for basal blood pressure control. Of particular interest, cGKI signaling contributes to long-lasting changes in neuronal plasticity, ranging from axonal pathfinding during embryogenesis to the adaptation of synaptic activity during learning and nociception.

These findings led to the speculation that cGKI might also regulate the 'plastic' processes associated with the phenotypic modulation of vascular smooth muscle cells (SMCs) during pathological vascular remodeling. To test this hypothesis, we have developed a tamoxifen-inducible Cre/lox system which allows one to induce somatic cGKI mutations selectively in SMCs of adult mice and to follow the fate of wild-type and cGKI-deficient SMCs during vascular remodeling. Our data indicate that a signaling pathway via cGMP and cGKI promotes the generation of SMCs with increased growth potential in vivo and in vitro, perhaps via effects on proliferation, apoptosis, and cytoskeletal dynamics. Thus, cGMP/cGKI signaling in vascular SMCs might promote pathological vascular remodeling processes, such as atherogenesis. Chronic activation of this pathway by cGMP-elevating drugs (e.g. organic nitrates, sildenafil) might result in undesired side effects, whereas its inhibition (e.g. by a cGKI inhibitor) might be an interesting approach to treat atherosclerosis.