P018 PI3Kgamma-CAAX breaks cell polarity in chemotaxing cells

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PI3Kgamma plays a crucial role for leukocyte migration and function. To study *in vivo* effects of PI3Kgamma activity we generated a “knock-in” mouse mutant expressing a constitutively active CAAX-boxed PI3Kgamma. Homozygous animals appeared viable, fertile but their leukocytes showed constitutive PtdIns(3,4,5)-P_3 (PIP3) production, increased proliferation and decreased apoptosis, though no signs of oncogenic transformation. Unexpectedly PI3Kgamma-CAAX leukocytes showed reduced peritoneal recruitment and impaired chemotaxis towards C5a, CCL5 and CSF-1, though random migration was not affected. In contrast to wild type controls, mutant macrophages neither polarized nor displayed chemokine-driven intracellular PIP3 localization at the leading edge. Moreover, in response to chemoattractants, mutant macrophages failed to activate Rac and showed a constitutive Rac GAP activity. Indeed, in wild type macrophages, chemoattractant stimulation causes activation of Rac but also a PIP3-dependent activation of Rac GAP causing its deactivation at the back side. Thus, constitutive PIP3 production breaks establishment and maintenance of cell polarity by interfering with a negative feed back loop deactivating Rac.