

**P036** Spatial and temporal control of Ras signalling through receptor-mediated increases in intracellular free calcium.

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Receptor-mediated increases in intracellular free calcium ( $[Ca^{2+}]_i$ ) are responsible for controlling a plethora of physiological processes. Increases in  $[Ca^{2+}]_i$  often occur as repetitive  $Ca^{2+}$  spikes or oscillations. Induced by electrical or receptor stimuli these  $Ca^{2+}$  spikes increase their frequency with the amplitude of the receptor stimuli, a phenomenon critical for the induction of selective cellular functions. We have reported that increases in  $[Ca^{2+}]_i$  mediate inactivation of Ras by modulating the activity of the Ras GTPase-activating proteins (RasGAPs) RASAL and CAPRI. These proteins are cytosolic, inactive RasGAPs that upon an elevation in  $[Ca^{2+}]_i$  undergo a rapid,  $C_2$  domain-dependent association with the plasma membrane, an association that leads to an increase in their RasGAP activity. Unlike CAPRI, which undergoes a transient plasma membrane association and does not sense receptor-mediated  $Ca^{2+}$  oscillations, the plasma membrane association of RASAL occurs in an oscillatory manner. This association occurs in synchrony with underlying receptor-mediated  $Ca^{2+}$  oscillations and is frequency modulated, such that upon increasing the amplitude of receptor stimuli, the frequency of RASAL membrane association is enhanced. Characterisation of such distinct  $Ca^{2+}$  sensors, tuned to detect different  $Ca^{2+}$  signals, has raised the issue of whether temporal dynamics of  $Ca^{2+}$  oscillations are optimised for efficient  $Ca^{2+}$ -mediated activation of Ras and downstream Ras signalling. Consistent with this we have shown that the frequency of  $Ca^{2+}$  oscillations are optimised for efficient activation of Ras and the ERK/MAPK cascade.