The receptor tyrosine kinase Tie2 is required for angiogenesis. Tie2 signalling, initiated by binding of the ligand Angiopoietin-1 (Ang1), results in the activation of many signal transduction pathways that act to produce a range of physiological effects on the cell. Depending on the cellular environment it is likely the cell will need to bias activation towards a subset of signalling molecules in order to produce a particular outcome e.g. migration or anti-inflammation. An emerging paradigm is that different signalling outputs are regulated by the intracellular localization of receptors and signalling molecules and potentially by their inclusion into unique molecular membrane microdomains, termed signalsomes. In physiologically relevant endothelial cells we have shown that following Ang1 stimulation, Tie2 is internalized, activates differing subsets of signalling molecules at specific locations within the endocytic pathway and localizes to a sub-population of signalling endosomes. The small GTPase rab5 is a master regulator within the early endocytic pathway and is converted to an active GTP bound form by guanine nucleotide exchange factors (GEFs). We have shown that over expression of one rab5 GEF, hRme-6, alters the kinetics of Tie2 signalling resulting in a downregulation of Akt signalling, and an upregulation of p38 MAPK signalling. Taken together our data supports a model in which the endocytic pathway and hRme-6 modulate Tie2 signalling and thus ultimately angiogenesis.