Nance Horan Syndrome-Like 1 (NHSL1) is a novel negative regulator of cell migration

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Abstract

Cell migration is essential for development, homeostasis and wound healing and its deregulation causes many diseases, which include cancer metastasis . The Scar/Wave complex is absolutely required for lamellipodia formation and is a key effector in cell migration. Efficient cell migration also requires precise fine-tuning of actin filament length and branching which are regulated by a number of actin binding proteins, which includes Ena/VASP and Scar/Wave. The Nance Horan syndrome is an X-linked developmental disease and affected males exhibit cataracts and developmental delay and mutations in the Nance Horan syndrome protein (NHS) causes these defects. NHS is only expressed in fetal brain, thymus, lung and kidney, whereas NHSL1 is ubiquitously expressed. We have identified NHSL1 as a novel Ena/VASP ligand and mapped two Ena/VASP binding sites within NHSL1. In agreement, NHSL1 colocalises with Ena/VASP proteins and also with the Scar/WAVE complex at the very edge of lamellipodia. Consequently, we found that NHSL1 coimmunoprecipitates with the Scar/Wave complex and show that this is mediated by a direct interaction between the SH3 domain of Abi and NHSL1. NHSL1 is a substrate of Abl kinases. However, the phosphorylation by Abl kinases does not regulate this interaction. In contrast, our data indicates that this interaction is positively regulated by Rac activity. Surprisingly we found that NHSL1 acts as a negative regulator of mammalian cell migration. We have previously shown that Lamellipodin positively regulates lamellipodia formation and cell migration via Ena/VASP and Scar/WAVE suggesting that NHSL1 interaction with both Ena/VASP and Scar/Wave may provide a negative feedback loop important for the temporal and spatial fine-tuning of the formation of lamellipodia for timely and controlled cell migration.