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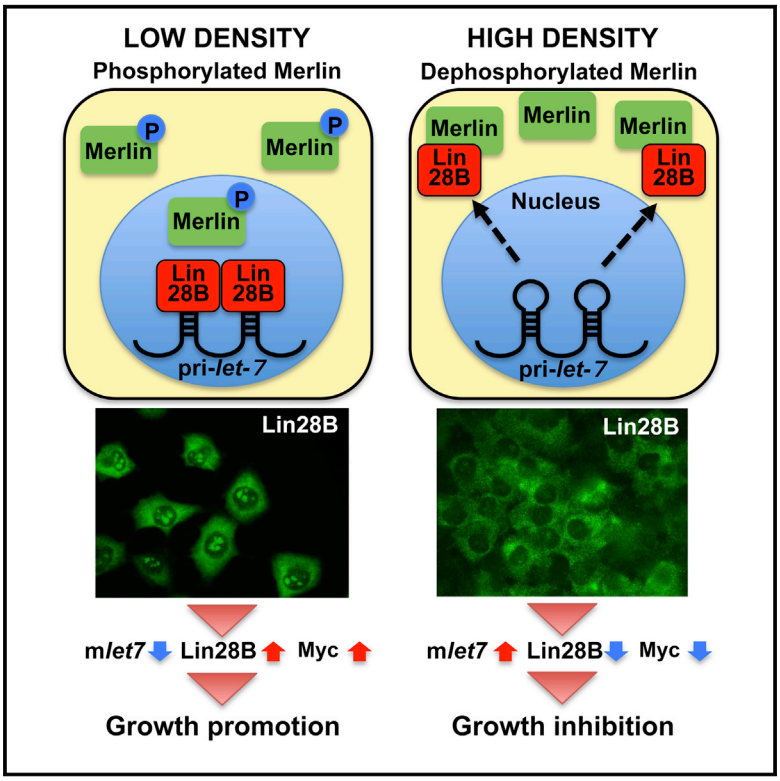
Merlin/*NF2*-Lin28B-*let-7* Is a Tumor-Suppressive Pathway that Is Cell-Density Dependent and Hippo Independent

Graphical Abstract



Highlights

- Lin28B, which inhibits *let-7* microRNA, is a key downstream target of Merlin/*NF2*
- At low cell density, phosphorylated Merlin/*NF2* does not bind to Lin28B
- Dephosphorylated Merlin/*NF2* sequesters Lin28B, inhibiting growth
- Merlin/*NF2* drives cell-density-dependent and Hippo-independent tumor suppression

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In Brief

Hikasa et al. reveal an essential growth-inhibitory mechanism, by which Merlin/*NF2* suppresses Lin28B function and promotes *let-7* biogenesis in a YAP1/TAZ-independent manner. Contact inhibition triggers Merlin/*NF2* dephosphorylation, which inhibits nucleolar/nuclear localization of Lin28B and induces pri-*let7* maturation, leading to cell growth inhibition. They suggest that Merlin/*NF2* thereby drives a cell-density-dependent tumor-suppressive pathway.

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Merlin/*NF2*-Lin28B-*let-7* Is a Tumor-Suppressive Pathway that Is Cell-Density Dependent and Hippo Independent

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SUMMARY

Contact inhibition of proliferation is critical for tissue organization, and its dysregulation contributes to tumorigenesis. Merlin/*NF2* is a tumor suppressor that governs contact inhibition. Although Merlin/*NF2* inhibits YAP1 and TAZ, which are paralogous Hippo pathway transcriptional co-activators and oncoproteins, it is not fully understood how Merlin/*NF2*-mediated signal transduction triggered by cell-cell contact exerts tumor suppression. Here, we identify Lin28B, an inhibitor of *let-7* microRNAs (miRNAs), as an important downstream target of Merlin/*NF2*. Functional studies revealed that, at low cell density, Merlin/*NF2* is phosphorylated and does not bind to Lin28B, allowing Lin28B to enter the nucleus, bind to pri-*let-7* miRNAs, and inhibit their maturation in a YAP1/TAZ-independent manner. This inhibition of pri-*let-7* maturation then promotes cell growth. However, cell-cell contact triggers Merlin/*NF2* dephosphorylation, which sequesters Lin28B in the cytoplasm and permits pri-*let-7* maturation. Our results reveal that Merlin/*NF2*-mediated signaling drives a tumor-suppressive pathway that is cell-density dependent and Hippo independent.

INTRODUCTION

Intercellular contact leads to inhibition of cell proliferation, a process called contact inhibition. Contact inhibition is essential for the maintenance of tissue homeostasis, and its disruption is characteristic of cancer (Hanahan and Weinberg, 2011). Merlin, also known as neurofibromatosis type 2 (*NF2*), is a major effector of contact inhibition and also a tumor suppressor gene (Curto et al., 2007; Morrison et al., 2001; Okada et al., 2005; Yi et al., 2011). The presence of inactivated Merlin/*NF2* in a variety of cancers in both mice and humans is evidence of Merlin/*NF2*'s potent tumor-suppressive activity (Li et al., 2012; Sekido, 2013).

Merlin/*NF2* is a FERM-domain-containing protein and serves as a linker between transmembrane proteins and a cell's actin cytoskeleton. Merlin/*NF2* inhibits mitogenic signal transduction, and several lines of evidence suggest that this growth-inhibitory role is associated with receptor-dependent pathways such as EGFR-RAS signaling (Benhamouche et al., 2010; Curto et al., 2007), Rac-PAK signaling (Kissil et al., 2003; Okada et al., 2005; Xiao et al., 2002), and HA-CD44 signaling (Bai et al., 2007; Morrison et al., 2001). Furthermore, there is genetic evidence in mice and flies that Merlin/*NF2* activates the tumor-suppressive Hippo pathway that is important for contact inhibition. This Hippo pathway activation leads to inhibition of the paralogous transcriptional coactivators YAP1 and TAZ, which are key regulators of cell proliferation (Hong and Guan, 2012; Pellock et al., 2007; Yu et al., 2010; Zhang et al., 2010). In addition, recent studies have demonstrated that nuclear Merlin/*NF2* inhibits the CRL^{DCAF1}-mediated proteolysis pathway critical for cell growth (Li et al., 2010, 2014). However, although it is clear that Merlin/*NF2* functionally interacts with a variety of signal-transduction pathways controlling cell proliferation and survival, it remains to be elucidated which pathway contributes to Merlin/*NF2*'s tumor-suppressive activity during contact-mediated inhibition of cell proliferation.

There is emerging evidence that the RNA-binding protein Lin28 is involved in cell growth and reprogramming, as well as in tissue homeostasis and cancer development (Rehfeld et al., 2015; Thornton and Gregory, 2012; Zhou et al., 2013). When Lin28 is overexpressed in mice, it enhances the metabolism of glucose and other bioenergetic molecules, leading to delayed onset of puberty, resistance to the development of obesity and diabetes, and enhanced tissue repair (Shyh-Chang et al., 2013; Zhu et al., 2010, 2011). In addition, mice with tissue-specific overexpression of Lin28 in neural crest, liver or small intestine develop tumors (Madison et al., 2013; Molenaar et al., 2012; Nguyen et al., 2014). Mechanistically, Lin28 regulates the translation of various mRNAs (Cho et al., 2012; Graf et al., 2013; Mayr and Heinemann, 2013; Shyh-Chang et al., 2013; Wilbert et al., 2012) and specifically suppresses the biogenesis of the *let-7* microRNA (miRNA) family (Roush and Slack, 2008; Viswanathan and Daley, 2010). *Let-7* miRNAs act as tumor suppressors by silencing the expression of critical oncogenes such as Myc,