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Relink *Stk11/Lkb1* in Stromal Cells to Peutz-Jeghers Syndrome

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Description

Lkb1 (Liver Kinase B1, encoded by Stk11) is a multifaceted serine/threonine kinase recognized as a tumor suppressor, regulating cell metabolism, cell polarity, cell fate, and cell survival [1-6]. Previous studies revealed that global knockout of *Stk11* in mice leads to embryonic lethality, indicating the pivotal role of Lkb1 in embryonic development [7]. Intriguingly, it is widely accepted that germline mutations in *Stk11* are strongly associated with Peutz-Jeghers Syndrome (PJS) in humans, an inherited disease characterized by Gastrointestinal (GI) hamartomatous polyposis and increased risks for multiple types of cancers [8]. Subsequently, the exciting findings to manifest PJS-like intestinal polyposis in mouse models with heterozygous deletion of *Stk11*, have fueled the researchers worldwide to pursue the specific role of *Lkb1* in the pathogenesis of PJS [9-11].

More and more conditional *Lkb1* deletion mouse models have been developed to open new avenues for further investigation of the cell types and signaling pathways involved in polyp formation. Surprisingly, deletion of *Lkb1* in intestinal epithelial cells results in increased susceptibility to colitis and suppression for microbial population, but shows no evidence of GI polyps in mice, even those 52 weeks of age [12,13]. These lines of evidence indicate the potential roles of nonepithelial *Stk11/Lkb1* in the development of PJS-associated GI polyps. To this end, multiple conditional knockout mouse models of Lkb1 in mesenchymal (stromal) cells have been generated, including Tagln-Cre (Smooth Muscle Cell (SMC)-specific), Fsp1-Cre (Fibroblast -specific), Twist2-Cre and Gli1-Cre (mesenchymal progenitor cell-specific) Nkx3.2-Cre (pan-mesenchymal cell specific), which suggest that *Lkb1* mutation in certain murine stromal cells could drive PJS-like GI polyposis N [14-16].

Our recent study further confirmed the critical role of mesenchymal *Stk11/Lkb1* in the pathogenesis of gastrointestinal polyposis [17]. We generated tamoxifen-inducible *Lkb1$^{flox/+}$;Myh11-Cre/ERT2 (Lkb1 Het)* and *Lkb1$^{flox/flox}$;Myh11-Cre/ERT2 (Lkb1 KO)* mice. We found that heterozygous rather than homozygous *Lkb1* deletion in murine mature SMCs is sufficient for the manifestation of PJS-like polyps, which is inconsistent with previous finding observed in mice with SMC-targeted inactivation of *Stk11* by Tagln-Cre [14]. PJS-like polyps, characterized by an arborizing smooth muscle core, abundant ECM deposition and augmented immune cell infiltration, were observed in *Lkb1* Het mice from 9 months post-tamoxifen treatment, in contrast to none developed in *Lkb1* KO mice till their death. Furthermore, *Lkb1$^{flox/flox}$;Pdgfrα-Cre/ERT2* mice, another mesen- chymal *Stk11/Lkb1* deletion model, also simulated historically similar polyps to those in *Lkb1* Het GI, as early as 2-3 months after tamoxifen treatment. Results supported the notion that Myh11^{+} or Pdgfrα^{+} mesenchymal cells may serve as an important cellular origin for PJS-like polyps.

To provide novel insights into the comprehensive cellular components and the underlying molecular mechanisms of the *Lkb1*-associated polyps, we performed a single-cell transcriptome atlas of *Lkb1*-associated polyps for the first time in *Lkb1$^{flox/+}$;Myh11-Cre/ERT2* mice. Clustering analysis revealed that there are polyposis-specific cell clusters and a higher portion of mesenchymal cells within *Lkb1* Het duodenum polyps, compared with normal GI tissues. As the largest cell population in duodenum, the epithelial cells from *Lkb1* Het polyp exhibited aberrant stem cell-like characteristics at an impaired differentiation state, along with an increment in expression of stem cell markers such as Cd44 as previously clarified but a decrement in mature enterocyte markers [15,18]. Of note, the up regulation of genes encoding secretory proteins of the gastric mucus barrier in those abnormal stem cell-like epithelial cells displayed the functional switch into a more secretary phenotype consistent with previous findings, which necessitates further research into the biological significance of *Lkb1* in GI homeostasis.

Interestingly, coupled with the reported Spp1-Cd44 axis promoting tumor progression and metastases we found that intercellular communication networks (Spp1-Cd44 or Spp1-Itga8/Itgb1) among the epithelial, mesenchymal/stromal, and immune cells contribute to polyposis process [19,20]. Besides, special focus should be given to the abundant immune cell infiltration in *Lkb1*-related polyps in our study and other studies. Previous study demonstrated that *Lkb1* deficiency in T cells is sufficient to promote the development of gastrointestinal polyps [13]. However, the underlying mechanism of deregulated inflammatory responses caused by *Stk11/Lkb1* inactivation in stromal cells and immune cells is awaited to further identified.

In general, it is the first time to conduct a single-cell transcriptome atlas of *Lkb1*-associated polyps, trying to elucidate the pathological microenvironment changes, variations in cellular constitutions and functionalities and possible signaling pathways in cell-cell interactions. Key questions remain to be answered about how mesenchymal *Lkb1* regulates epithelial cell fate/state in *Lkb1*-associated polyps. Further research is warranted in the aim of yielding clinical benefits for patients with PJS.

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