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A Tale of Two Elabela Null Mice

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Abstract

Elabela, the second peptide ligand for APLNR, was previously found in lower vertebrates to be critical for endoderm and cardiac development. Two new studies report on the phenotypes of Ela null mice, ranging from defective embryogenesis to preeclampsia that provide new insights and raise greater intrigue into this cardiometabolic pathway.

Keywords

preeclampsia; embryo development; GPCR; APLNR signaling

G-Protein Coupled Receptors (GPCRs) as a class are utilized by almost every cell type in the human body, and remain the most widely targeted molecules by the pharmaceutical industry. They have the capacity to respond to diverse environmental stimuli, ranging from peptides and small molecules to light and hemodynamic forces, and facilitate an extensive network of downstream signaling pathways. As the landscape of GPCRs and their ligands continues to expand, Elabela (Ela, also referred to as Apela, or Toddler) recently emerged as a second ligand for APLNR (APJ or Apelin Receptor) [1, 2], a GPCR that has widespread implications in development and disease. While the two new studies of *Ela* null mice [3, 4] provide insight into the previously observed differences between the developmental phenotypes of the *Apelin* (*Apln*, first identified ligand for APLNR) and *Aplnr* null mice [5, 6], they raise additional questions as we continue to seek mechanistic insights and therapeutic implications of this pathway.

APLNR signaling is important for a wide spectrum of mammalian homeostatic and disease processes, including cardiovascular development [5, 7], atherosclerosis [8] and diabetes [9]. Mice lacking *Aplnr* exhibit incomplete penetrance of embryonic lethality, with very few mice surviving to adulthood [5], however, mice lacking *Apln*, the canonical APLNR ligand, are viable and fertile [6]. This discrepancy has for years sparked discussions of yet unknown APLNR ligands which may promote distinct temporal or tissue specific aspects of the APLNR signaling cascade. Discovery of Ela as the second ligand for APLN addressed some

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of the questions regarding the remarkable discrepancies between the phenotypes of the *Apln* and *Aplnr* null mice. Furthermore, these studies, which were performed in lower vertebrates, suggest that apln may be predominantly required in disease contexts, while ela may participate in the embryonic development functions of APLNR signaling [1, 2].

The two new studies sought to determine the role of Ela through the generation and phenotyping of *Ela* null mice [3, 4]. In the first study from the Reversade group, mouse embryos lacking *Ela* were found to have up to 50% incidence of embryonic lethality, and presented with a host of defects that were contributed to improper establishment of the fetal-maternal circulation, such as under-developed yolk sac vasculature, impaired cardiac tube looping, defective chorio-allantoic fusion and compromised hematopoietic progenitor specification [4]. *Ela* null placentas were found to have thin labyrinths, poor vascularization, increased apoptosis, decreased proliferation, and elevated expression of hypoxia related genes. Ela was found to suppress tip cell gene expression in the placenta, including *Apln*, and promote pruning and maturation of the vascular network. These data support the view that, at least in mammals, Ela plays a primary role in placental development, which can secondarily affect development of the embryo proper, in addition to controlling embryo specific APLNR signaling. These observations led the group to examine the physiological effect of poor placental development in pregnant females. *Ela* null pregnant females developed hallmarks of preeclampsia (PE), including elevated systolic blood pressure, proteinuria and glomerular endotheliosis. The incidence of lethality in *Ela* null embryos was further increased when pregnant mother and embryos were both null for *Ela*.

The study by the Hadjantonakis group found a much lower incidence of embryonic lethality in *Ela* null embryos compared to the Reversade group (10% versus 50%) [3]. In addition, whereas Reversade group described a remarkable impact on embryonic viability depending on the genotype of the mother (survival of *Ela* null mice was much lower in those mice weaned from *Ela* null mothers), such was not the case in the mice generated by the Hadjantonakis group. Although PE was not directly assessed in the Hadjantonakis study, there was demonstration of thinner allantois in a subset of the *Ela* null embryos, which is similar, albeit less severe, to the phenotype observed by the Reversade group. Detailed analyses of the cardiovascular system with 3D microCT demonstrated higher penetrance of vascular malformations such as unremodeled yolk sac and/or vitelline vessels, but many of these embryos appeared to recover later on in development. Finally, gene expression profiling from the Hadjantonakis group highlights upregulation of erythroid and myeloid genes, which differ from the hypoxic responsive genes identified by the Reversade group, but a direct comparison of the gene expression profiling analyses would be needed to fully characterize the similarities and differences. Overall, these findings underscore the intriguing possibility that further levels of regulation and additional molecular players are likely to be involved in the complex APLNR signaling pathway.

The differences in penetrance of the phenotypes aside, both of these studies provide crucial insights into the role of ELA during pregnancy and embryogenesis, while demonstrating multiple differences between ELA and APLN. Nevertheless, there are still questions that remain unanswered. First, while no secondary receptor has ever been identified for APLN, the suggestion that ELA may act through another receptor will need further investigation

[10]. Second, with respect to PE, multiple previous studies have suggested involvement of APLN-APLNR signaling pathway; with demonstrated PE in *Ela* null mice and rescue of this phenotype with exogenous ELA administration, future studies to identify and selectively activate the therapeutic aspects of APLNR signaling may pave the path towards targeting this pathway as future therapy. Finally, it would be critical to define the crosstalk between ELA/APLN-APLNR signaling and other disease-relevant pathways, not just in PE but in other disease contexts in which APLNR is being considered as a therapeutic target.

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