IPO-04  Non-genetic risk factor for Hirschsprung disease

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The etiology of Hirschsprung disease has been genetically studied for decades. There are a lot of molecules and genes involved in the mechanism which results in disorder of enteric nervous system (ENS) development like Hirschsprung disease. Raldh2 \(-/-\) mouse which lacks retinoic acid (RA) leads to severe defect in developing gut. Although this suggests RA might affect ENS development, mechanism has not yet been understood. Firstly we evaluated the gene expression patterns which are related to retinoid metabolism in the developing gut by in situ hybridization. Most of genes are expressed in ENS and other region next to ENS. However Rarb which is prominently retinoid responsive gene is not expressed by enteric neuron at birth. To define the role of RA in developing gut, we cultured ENS precursors which are dissociated from embryonic gut in RA sufficient or deficient media. Interestingly neurite outgrowth is repressed under RA sufficient condition, although RA facilitates differentiation, proliferation and migration. The results are interpreted that RA facilitates migrating in developing gut by reducing neurite outgrowth because neurite easily moves forward. To test this interpretation, we also analyzed migration by using RBP \(-/-\) mouse which can be depleted RA easily. Mice fed with RA depleted food were analyzed at E14.5, shortly after ENS normally colonizes the colon. Almost all mice had distal colon aganglionosis. These results indicate RA is a non-genetic risk factor for Hirschsprung disease.