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INTERSTITIAL CELLS OF CAJAL AND GUT MOTILITY IN ABDOMINAL WALL DEFECT MICE LACKING AORTIC CARBOXYPEPTIDASE-LIKE PROTEIN: EFFECTS OF PRO-INFLAMMATORY CYTOKINE IL-8

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Aim of the Study: Gastroschisis-related intestinal dysfunction may be secondary to deficient interstitial cells of Cajal (ICC) due to bowel exposure to amniotic fluid. We aimed to determine ICC/enteric neuron architecture, cell numbers and gut motility in the aortic carboxypeptidase-like protein (ACLP) knockout mouse model of abdominal wall defect (AWD), in which the gut is exposed to exocoelomic fluid (rather than amniotic fluid as in gastroschisis), and the effects of in-utero IL-8 injection.

Methods: Experimental groups included untreated controls/AWD, IL-8 injected controls/AWD. IL-8 was injected (controls: amniotic cavity; AWD: exocoelomic cavity) at E16.5 following resolution of physiological herniation. Ileum was collected at E18.5, whole-mount immunostained for ICC (anti-CD117) and enteric neurons (anti-PGP9.5), and imaged using confocal microscopy (n=10 per group). Mean cell numbers/stack were compared with ANOVA. Ileal motility (n=5 per group in control, AWD, AWD/IL-8) was video recorded in an organ bath, using MATLAB software to create spatiotemporal maps and perform incremental vertical slice analysis of percentage ileal diameter change and contraction frequency. Data mean±SEM.

Results: Enteric neuron architecture and number were similar in all groups. ICC exhibited mature cell networks in all groups (Figure, maximum intensity project). ICC numbers (Figure) were significantly reduced in untreated AWD (80±2.1) vs. untreated controls (90±2.5, p=0.029). IL-8 injection was associated with decreased ICC reaching significance in controls (69±2.7, p=0.0001 vs. uninjected), but not AWD (72±3.3, p=0.37). Motility in AWD and IL-8 injected AWD expressed a lower percentage change in mean diameter (Figure) and lower contraction rate compared to controls.

Conclusions: ICC numbers are decreased by failure of abdominal wall closure, and by exposure of normal bowel to an inflammatory environment. Motility studies revealed more rudimental motility patterns in untreated/injected AWD fetuses. As ICC are important determinants of intestinal motility, these findings may have implications for the development of gastroschisis-related intestinal dysfunction.