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DELIVERY OF VASCULAR ENDOTHELIAL GROWTH FACTOR WITH BIOCOMPATIBLE NANOPARTICLES REVERSES STRUCTURAL ARTERIAL ABNORMALITIES IN THE NITROFEN RAT MODEL OF CONGENITAL DIAPHRAGMATIC HERNIA

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Aim of Study: The aim of the study was to determine whether gradual prenatal intra-pulmonary delivery of vascular endothelial growth factor (VEGF), using nanodiamonds (ND) that release their cargo over 48-72 hours, has salutary effects against pulmonary arterial structural abnormalities in experimental congenital diaphragmatic hernia (CDH).

Methods: CDH was induced in pregnant Wistar rats by administration of nitrofen. Maternal hysterotomy was performed at E19, and ND (75µg/mL in 50µL vehicle/saline) were administered into the fetal trachea followed by tracheal occlusion (TO). ND were conjugated with recombinant VEGF164 (ND-VEGF; 2µg/mL VEGF164). Blinded assessment of lung-to-body weight ratio (LBWR) and pulmonary vascular morphometry was performed at E21.5 in CDH offspring. To examine the mechanism of action of VEGF in this setting, an inhibitor of the VEGF-receptor-2 (KDR/Flk-1) was co-administered (SU5416; 2mg/kg). Statistical analysis was performed using 1-way ANOVA with Bonferroni tests.

Results: ND-VEGF+TO was associated with improved lung growth (LBWR: 5.5±0.3%), which was significantly greater than that observed in unconjugated VEGF+TO (3.5±0.2%; $p<0.01$), raw ND+TO (3.3±0.2%; $p<0.01$), vehicle+TO (3.6±0.2%; $p<0.01$) and sham (2.0±0.2%; $p<0.001$), but similar to healthy controls (5.3±0.2%). Moreover, ND-VEGF+TO decreased muscularisation of pulmonary arterioles (≤50µm diameter; medial thickness: 20.3±0.9%) compared to other treatment groups (VEGF+TO: 26.8±0.8%, $p<0.01$; raw ND+TO: 26.9±1.0%, $p<0.01$; vehicle+TO: 26.9±1.2, $p<0.01$; sham: 36.9±1.2%, $p<0.001$). Morphometric parameter values in ND-VEGF+TO animals were comparable to these observed in healthy controls. Co-administration of SU5416 abrogated the beneficial effects of ND-VEGF, but did not affect outcomes in any other of the treatment groups.

Conclusions: Prenatal intra-pulmonary delivery of VEGF with biocompatible nanoparticles reverses CDH-associated structural arterial abnormalities via KDR/Flk-1 activation when used in combination with TO. The lack of measurable effects of unconjugated VEGF suggests that gradual release, mimicking the spatial and temporal expression of VEGF in normal lung development, is a requirement for bioactivity in this setting.