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BIRTH OF THE FIRST "HUMAN BA ORGANOIDS"- HINTING ON THE AETIOLOGY AND DISEASE PROGRESSION OF ISOLATED BILIARY ATRESIA?

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Aim of the Study: Biliary atresia (BA) accounts for most paediatric liver transplantations, yet no research model exists to decode the multiple aetiological mechanisms of BA.

Establishment of "human organoids" from liver biopsies were first reported on patients with a1-antitrypsin deficiency and Alagille syndrome in 2015. Such organoids recapitulated their respective *in vivo* pathologies, and could be expanded continuously from a single liver stem cell to an organized 3-D structure resembling mature bile ducts in the dish for studying developmental processes or derivation of human cells for manipulation / RNA-seq.

We aimed to establish the unprecedented "human BA organoids" and harness their potential to elucidate BA aetiologies and test therapeutic options to ameliorate post-Kasai disease progression.

Methods: Wedge biopsies (Bx) (50x50mm) were obtained from eight non-syndromic BA patients during laparoscopic cholangiography (LC), two BA liver explants at transplantation (LTx), and three paediatric patient controls (2 choledochal cysts (CC), 1 hepatoblastoma (HB)). Personalized organoids were established for each patient, and cultured for one to three months. Cultures were passaged when organoids grew beyond the size limit.

Main Results: Organoids were successfully established from all controls and six BAs (at LC). The remaining two were associated with some prenatal causes. Organoids could not be established from liver explants. Differences in morphology and growth rate (p=.012) were observed between the controls and BAs (Table 1).

Conclusion: Novel BA organoids were established capturing morphological and dynamic growth differences from controls. Failed organoid establishment might indicate the liver condition at disease stages (Kasai vs LTx) and mechanistic differences in BA suggestive of prenatal and postnatal causes. Robust success in establishing organoids for isolated BA from biopsies at diagnosis proves the potential of the organoids in modelling the disease course during the Kasai-to-LTx, allowing further investigations into the aetiologies and therapeutic possibilities for BA.

	Diagnosis	Age at Bx	Male(1)/ Female(2)	Bx at LC(1)/ LTx(2) (for BA)	Prenatal causes (for BA)	Successful(1)/Failed (0) organoid establishment	Organoid growth rate
1	BA	60 days	2	1	--	1	No Passage after 3 months
2	BA	67 days	1	1	--	1	No Passage after 3 months
3	BA	68 days	2	1	--	1	No Passage after 3 months
4	BA	76 days	1	1	--	1	No Passage after 3 months
5	BA	91 days	1	1	--	1	No Passage after 3 months
6	BA	118 days	1	1	--	1	No Passage after 3 months
7	BA	51 days	2	1	Cystic BA	0	--
8	BA	77 days	2	1	Maternal CMV infection during pregnancy	0	--
9	BA	8 month	1	2	--	0	--
10	BA	7 months	1	2	--	0	--
11	CC	13 days	1	--	--	1	Passage on Day30
12	CC	6 years	1	--	--	1	Passage on Day20
13	HB	2.9 years	1	--	--	1	Passage on Day24

Table 1. Individual patient details