Seminars in Pediatric Surgery (2011) 20, 136-144

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SEMINARS IN PEDIATRIC SURGERY

Embryology of the early foregut

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KEYWORDS
Development;
Esophageal atresia;
Esophagus;
Foregut;
Larynx;
Pharynx;
Scanning electron microscopy (SEM);
Trachea

In embryology, no agreement exists how the early foregut differentiates into the respiratory tract and the intestinal tract. In particular, the formation of the early lung anlage as well as the process of separation of trachea and esophagus remains unclear. This process is explained in a rather schematic way and aims more to explain pathologic findings, whereas true embryologic investigations are extremely rare in this field. Here, scanning electron microscopy of the normal foregut development illustrates the steps, which finally leads to the development of larynx and trachea on the one hand, and pharynx and esophagus on the other hand. This study was performed in chicken embryos in accordance to the developmental stages described. As the main results from these illustrations show, we found no evidence for lateral foregut ridges inside the undivided foregut chamber and no fusion of lateral foregut components to form a trachea-esophageal septum.

Among embryologists as well as pediatric surgeons, no agreement exists on the differentiation of the early foregut into the respiratory tract and the intestinal tract.[1,2] In particular, the formation of the early lung anlage as well as the process of separation of trachea and esophagus remains unclear.[2]

In this work, scanning electron microscopy (SEM) of the normal foregut development is used to illustrate the steps, which finally lead to the development of larynx and trachea on the one hand and pharynx and esophagus on the other. These illustrations represent an atlas of the foregut development, providing a 3-dimensional impression of normal embryonic foregut differentiation. This study was carried out in series of chicken embryos according to the developmental stages described by Hamburger and Hamilton (Table 1).[3]

Primitive foregut development

Visible differentiation of the foregut starts at chick embryonic day 1.5 (Figure 1). In this age group, the head, the pericardial cavity and the heart, are developed. The foregut can be subdivided in a cranial and caudal part. The caudal part is located behind the heart and the pericardial cavity and opens into the midgut via the anterior intestinal port. The cranial part of the foregut extends into the head region with the bucco-pharyngeal membrane as cranial border. In the first set of illustrations the developmental changes in the caudal foregut are shown that lead to the formation of the early lung anlage (Figures 2 and 3).

The developing foregut from a ventral view

After removal of the heart and the dorsal serosa of the pericardial cavity, the epithelium of the early foregut anlage can be seen (Figure 2A, stage 10). There are no clear signs of primitive foregut organs visible beside a small fold that marks the first appearance of a pharyngeal pouch. The caudal end of the foregut widens to form the anterior intestinal port.

In stage 12 the shape of the foregut changes (Figure 2B). At its caudal end, the foregut is narrowing to the region of the anterior intestinal port. The pharyngeal pouches are now more pronounced. The anlage of the thyroids can be seen as

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doi:10.1053/j.sempedsurg.2011.03.004

Table 1 Developmental Stages as Described by Hamburger and Hamilton

Stage	Embryonic Day (ED)	Development	Figures
10	1.5	The head, the pericardial cavity and the heart are developed. The foregut can be subdivided in a cranial and caudal part. The caudal part is located behind the heart and the pericardial cavity and opens into the midgut via the anterior intestinal port. The cranial part of the foregut extends into the head region with the bucco-pharyngeal membrane as cranial border.	1, 2A
11	1.75	The epithelium of the early foregut anlage is seen. There are no clear signs of primitive foregut organs visible with the exception of a small fold which marks the first appearance of the pharyngeal pouch. Signs of a lung anlage are missing. Cranial to the pharynx pouch and distal, the liver diverticulum is seen.	5A
12	2	The caudal end of the foregut widens to form the anterior intestinal port. At its caudal end the foregut becomes smaller in the region of the anterior intestinal port. The pharyngeal pouches are more pronounced. The anlage of the thyroids can be seen as a pouching in the midline of the ventral foregut between the 1st and 2nd pharyngeal pouch. The lung anlage is lacking.	2B, 3A
15-17	2.5	Directly caudal to the pharyngeal pouches 2 folds appear, which grow into the foregut and form the anlage of the larynx. At the caudal end of the foregut, the liver anlage is seen. Halfway, between the liver anlage and the anlage of the larynx, the very early anlage of the respiratory tract is seen as an oblique shallow fold. Between the larynx folds cranially and the outlet of the esophagus caudally, the "undivided" foregut chamber can be seen.	2C, 3C, 5B
18	2.75	The anlage of the esophagus and stomach appears. Cranial to that area, an "undivided" foregut chamber can be seen. The lung bud is more advanced and also the liver anlage shows differentiation into two ducts.	3B, 3D
19/20	3	The definitive anlage of the lung buds can be seen as a bilateral swelling of the foregut. In addition, the esophagus anlage can be identified with its narrower lumen. The "undivided" foregut is clearly visible.	2D, 4A, 5C, 6A, 6C
20/21	3.5	The tracheal anlage appears as a broadening of the ventral foregut. This anlage extends cranially from the larynx to the offspring of the bronchi and is still part of the "undivided" foregut chamber.	4B, 6D, 7B
22/23	4	The trachea is seen for the first time as a partially isolated structure. Its cranial portion is still part of the foregut chamber. In this age group the trachea is still short and has a triangular shape. The "undivided" foregut chamber becomes smaller but never disappears.	4C, 4D, 5D
24/25	4.5	The trachea is now a completely isolated structure. The esophagus is clearly separated from the pharynx by the dorsal foregut fold. The differentiation of the distal foregut into its structures larynx/ pharynx/ trachea/ esophagus is complete.	4E
26	5	The "undivided" foregut chamber becomes smaller but never disappears. It will be incorporated into the larynx as the pharyngo-tracheal canal. The tip of the trachea-esophageal fold never reaches the laryngeal folds. The borderline between the pharynx and the esophagus is represented by the dorsal fold of the foregut.	5E, 6B

a pouching in the midline of the ventral foregut between the first and second pharyngeal pouch. Neither the lung anlage nor the anlage of the liver exists at this stage.

In stage 15, the changes of the foregut shape now become obvious (Figure 2C). Directly caudal to the pharyngeal pouches 2 folds appear, which grow into the foregut and form the anlage of the larynx. At the caudal end of the foregut, the liver anlage appears. Halfway between the liver anlage and the anlage of the larynx, the very early anlage of the respiratory tract is seen as an oblique shallow fold. In stage 19/20, the definitive anlage of the lung buds can be seen as a bilateral swelling of the foregut (Figure 2D). In addition, the esophagus anlage can be identified with its narrower lumen.

The developing foregut from a dorsal and lateral view

In Figure 3A, B the changes of the foregut shape are illustrated from a dorsal view. Note the development of the lung buds as a bilateral swelling of the ventral foregut. In the area where the foregut becomes smaller, the anlage of the esophagus/stomach appears. Cranial to that area, an "undivided" foregut chamber can be observed (Figure 3B).

In Figure 3C, D the changes of the foregut shape are illustrated in a view from lateral and left. The early respiratory anlage is seen as a small and very shallow out-pouching of the ventral foregut. The liver anlage presents as a diverticulum, which projects ventrally just cranial to the anterior intestinal