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Original Research

Bronchial tree of the human embryo: categorization of the branching mode as monopodial and dipodial

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ABSTRACT:

Aim: The purpose of this study was to investigate the manner in which the proximal, lobar, segmental and subsegmental bronchus of the human lung diverge during the embryonic period. **Materials & methods:** Phase-contrast X-ray computed tomography was employed to acquire imaging data from a total of 40 samples ranging from Carnegie stage (CS) 15 to CS23. The image data was used to reconstruct the three-dimensional bronchial trees of all samples. The lobar bronchus, segmental bronchus and subsegmental bronchus were examined. **Results:** The branching mode of the analysed bronchi was categorised based on whether the progenitor bronchus was divided after the generation of the analysed bronchi, following the calculation of each bronchus length. Monopodial branching was employed to establish all lobar bronchi. Twenty bifurcations were analysed to determine the branching mode of the segmental and subsegmental bronchi. Seventeen bifurcations were classified as monopodial branching, two bifurcations were not classified as any branching pattern, and the sole lingular bronchus that formed a bifurcation from the left superior lobar bronchus was classified as dipodial branching. The left superior lobar bronchus did not shorten from CS17 or CS18, when the child branch was generated, to CS23. **Conclusion:** The lobar bronchus and segmental bronchus exhibit similar branching modes in the mouse lung and human lung; however, the subsegmental bronchi exhibit distinct branching modes. Additionally, there was no evidence of remodelling, including the bronchus' shrinkage, during the analysis period. The three-dimensional reconstructions enabled the precise calculation of the bronchus length, thereby enhancing our understanding of the branching morphogenesis in the human embryonic lung.

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INTRODUCTION

The lungs and kidneys, among other organs, are characterised by intricate structures that are the result of a series of bifurcations. The diagnosis and treatment of congenital anomalies are contingent upon an understanding of branching morphogenesis. Nevertheless, the process of morphogenesis is not widely recognised. Various kinds of branching mode categorizations have been proposed in previous studies to describe these bifurcations. Palmer introduced the human lung's three branching modes: dichotomous branching, trichotomous branching and lateral budding.[1] Metzger et al proposed the following three patterns for rodent bronchi: orthogonal bifurcation, planar bifurcation, and domain branching. The three primary branching modes identified in real-time analyses of mouse kidneys are lateral branching, terminal trifid branching, and terminal bifid branching.[2] Despite the distinctions between the analysed species or organs, these studies demonstrated that two simple and essential branching modes, monopodial branching and dipodial branching, are shared among all of these species. The tip of the bronchus is bifurcated with dipodial branching, while child branches (CBr) are generated at the sidewall of the primary branch (PBr) with monopodial branching. The former mode is associated with domain branching, while the latter mode is associated with planar and orthogonal bifurcation.[3]

The human bronchial tree underwent intricate morphological alterations during the embryonic period.[4]The lobar bronchi appeared to be formed monopodially, and the human embryonic bronchial tree appeared to have a similar structure until the subsegmental bronchus were observed. These are the four following two characteristics of the human embryonic bronchial tree.[5] The trachea and lobar bronchi, in particular, did not exhibit any individual

differences. Individual variability was observed in the segmental and subsegmental bronchi of each sample. The quantity of these variations was minimal in comparison to the adult lung studies that have reported these variations, despite the fact that 14 variations were identified at the segmental level.[6] Furthermore, the bronchus that comprise the bronchi in children did not undergo a significant shift in length during development; in other words, the bronchi did not abruptly contract during the embryonic period. Consequently, the bronchus length can be used to classify the branching modes as monopodial or dipodial.[7]

The goal of the current investigation was to investigate the manner in which the proximal, lobar, segmental, and sub-segmental bronchi of the human lung diverge during the embryonic period.

MATERIALS AND METHODS

The Collection consisted of approximately 200 human embryos that were preserved at the Congenital Anomaly Research Centre. The majority of the pregnancies were terminated during the first trimester due to socioeconomic factors. At that time, parents were not compelled to provide written informed consent. Rather, the parents of the participants provided verbal informed consent to deposit these specimens, and the assent of each participant was recorded in the medical record. All samples were de-identified and anonymized. The criteria of O'Rahilly and Muller were employed to measure, evaluate, and stage the embryos that were brought to the laboratory for abortion.[8]10% formalin was employed to preserve whole embryonic samples. A total of 40 human embryos between Carnegie stage (CS) 15 and CS23 were selected from the Collection. Anomalies and overt damage were absent from all samples. The alveoli were not inflated for imaging purposes.

Image acquisition and three-dimensional reconstruction

In summary, specimens were viewed using a crystal X-ray interferometer in conjunction with a phase-contrast imaging system. The vertical wiggler beam was the location where the system was installed. Serial two-dimensional and reconstructed three-dimensional images were employed to precisely analyse phase-contrast X-ray computed tomography data from selected embryos. Amira software version 6.2.0 was employed to reconstruct the bronchial tree structure for all samples. The airway's centre was linearly observed using the centerline module. Subsequently, the bifurcation point at the base and tip of the swellings was manually plotted to rectify the observation. The terms "node" and "branch" were defined during this investigation. The node was either the terminal point or the point at which bifurcation occurred. The branch was the trunk of the bronchus, which was bounded by two nodes. The PBr and CBr were the components of the analysed bifurcation.

Developmental phase of the bronchial tree during lobar bronchus formation

Morphological characteristics were employed to identify the subsequent three developmental phases of the embryonic bronchial tree during the formation of the lobar bronchus. The primary bronchus did not exhibit any lobar enlargement during phase 1. An almost symmetrical Y shape was achieved by the primary bronchus. The bronchus experienced lobar swellings that emerged from the centre of each bud during phase 2. The right superior lobar bronchus (RSLB) diverged during phase 3. All five distinct lobar swellings were present in the bronchus. The primary bronchi on the right and left exhibited the typical asymmetry. All 14 samples at CS15 and CS16 were categorised into one of these three phases.

Categorization of the branching mode based on length

The present study presumed that the degree of development was reflected in the branch length and the presence of CBr. Consequently, in order to classify the branching mode, we presented a graph in which the branch lengths were arranged in accordance with the magnitude and presence of CBr. The flowchart elucidates the categorization procedure. The PBr length (and CBr length if already generated) of the analysed bifurcation of all individual samples were measured. The orthogonal coordinates of the voxels of each reference point were used to calculate the length of each branch using MATLAB (version R2018a; MathWorks, Natick, MA, USA) algorithms. Data from all samples were categorised into two categories: a no-child group (NC) and a two-child group (TC). Bifurcations that generated no CBr and two CBr were categorised into the NC and TC groups, respectively. When the PBr of the analysed bifurcation was absent and the CBr generated additional descendant branches, data were excluded. Consequently, the NC group's data were sorted based on the length of the PBr [PBr(NC)], whereas the TC group's data were sorted based on the combined length of the PBr [PBr(TC)] and CBr. Finally, the NC and TC graphs were combined.

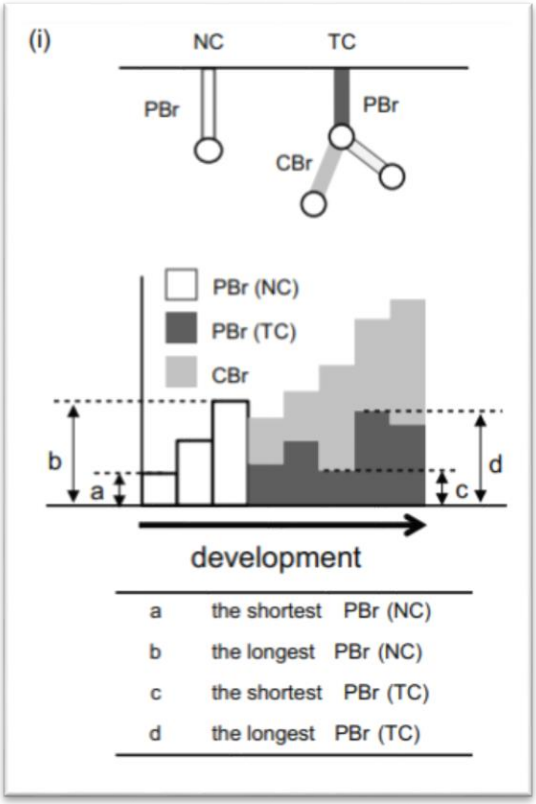

Figure 1: Branch lengths were according to the size and presence of CBr

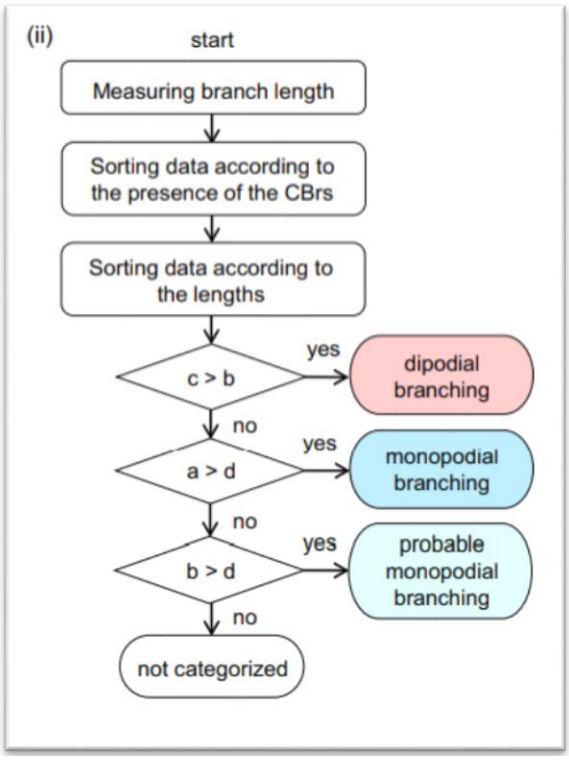

Figure 2: Categorization flowchart

The branching mode was classified as monopodial or dipodial based on whether the length of the PBr was divided following the generation of the CBr. The branching mode of an analysed bifurcation was classified as dipodial branching when the shortest PBr(TC) length was greater than the longest PBr(NC) length. The mode was defined as monopodial branching when the shortest PBr(NC) length was greater than the longest PBr(TC) length (a>d).

RESULTS

Branching mode of the lobar bronchi

The samples were analysed during phases 1 and 3 to classify the branching mode of the lobar bronchus. Our findings indicated that lobar bronchi were formed using the monopodial branching mode by comparing the PBr length before and after CBr generation. Probable monopodial branching consisted of two bifurcations (RMLB and LSLB), while monopodial branching consisted of one bifurcation (RSLB).

Table 1: Categorization of the branching mode of the lobar bronchus

Bifurcation	PBr(NC)/PBr(TC)/CBr	PBr(NC) (µm)			PBr(TC) (µm)			Categorization
		a		b	c		d	
RMLB	RPBB/temRMB/RIB	400		804	412		501	mono
RSLB	temRMB/RMB/IB	405		512	162		345	mono
LSLB	LPBB/LMB/LIB	357		756	245		535	mono

Deducing the branching mode of the segmental and subsegmental bronchi

Twenty bifurcations were examined. One bifurcation was classified as monopodial branching, while 16 were classified as probable monopodial branching. The sole lingular bronchus that bifurcated from the LSLB was classified as dipodial branching. The remaining two bifurcations were not classified as any branching mode.

The LSLB length appeared to increase progressively following the formation of CBr, eventually reaching 345 µm. The sample's shortest LSLB (157 µm) was approximately equivalent to the sample's longest LSLB(NC) (149 µm). Consequently, the LSLB length did not decrease, despite the fact that the peripheral branches repeatedly bifurcated.

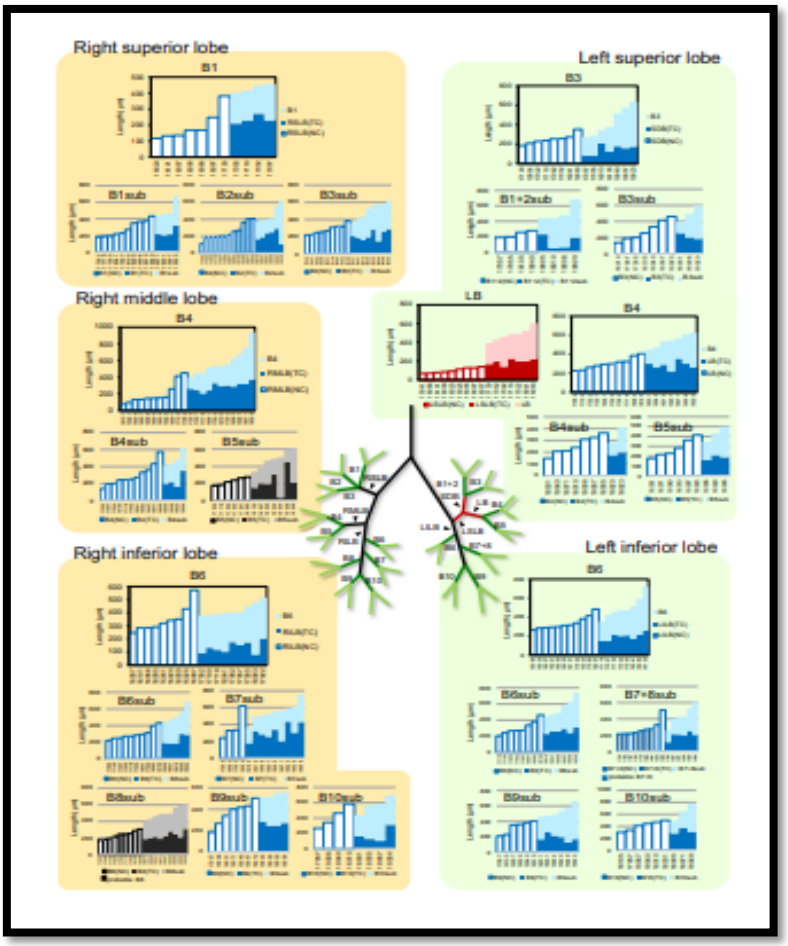

Figure 3: Branching mode categorizations of segmental and subsegmental bronchi

DISCUSSION

The entire lung space must be occupied by the two branching modes, monopodial and dipodial. The end branches would be arranged at the margin if the bronchial tree was formed with only dipodial branching.[9]Monopodial branching facilitates the filling of the lung interior. The central structure of the bronchial tree is generated by monopodial branching, while the periphery and interior are formed by dipodial branching, as evidenced by a previous study.[3]

Consequently, the morphogenesis of the human bronchial tree will be clarified through the categorization of the two branching modes.

Streeter reported that the lobar bronchus of the human embryonic lung sprout monopodially during CS15.[5] The results of the previous report regarding the branching mode of the lobar bronchus were estimated solely on the basis of visual assessments. However, our study statistically verified these findings by utilising length measurements.

It was discovered that the branching modes of the murine and human lung exhibit both similarities and differences in the current study. The central bronchi, lobar bronchus and segmental bronchus in mouse lungs were formed through monopodial branching, which is referred to as domain branching, as demonstrated by Metzger.[3] Similarly, our data demonstrated that the human lungs were characterised by the formation of lobar and segmental bronchi with monopodial branching. In rodents and humans, the lobar and segmental bronchi appear to be formed with a similar pattern (monopodial branching), according to the current study. Nevertheless, the subsegmental bronchus exhibited a distinct branching mode. The subsegmental bronchus, the second-generation bronchus of the lobar bronchus, in rodents was formed through both monopodial and dipodial branching, according to Metzger et al.[3] Nevertheless, our findings indicate that the subsegmental bronchus in the human bronchial tree were exclusively the result of monopodial branching. In other words, the branching mode of the lobar bronchus and segmental bronchus in the murine bronchial tree was consistent with that of the human lungs. However, the branching mode of the subsegmental bronchus differed between mice and humans in terms of both the branching mode and the structural features thereof. The branching pattern of the rodent lung is relatively stereotypic, whereas the branching tree in humans exhibits a greater degree of variation.[10,11] Even during the embryonic period, this variability in human lungs has been documented.[12,13,14] Additional research is required to explain the variations in the mechanism of peripheral bronchi in the lungs of mice and humans.

A remodelling mechanism known as node retraction was previously identified in the rodent kidney.[15] The PBr shortens following the generation of the CBr during node retraction. The branching mode would be incorrectly classified if this remodelling were to take place in the human lungs. Nevertheless, Watanabe et al[2] documented the morphogenesis of the mouse kidney until the eighth generation, but they did not report node retraction. In a previous study, Lindstro¨m et al[15] ascribed this discrepancy to the insufficient culture period for node retraction.[2] The LSLB length did not decrease during our observation of the LSLB's morphogenesis in the present study until CS23 (the ninth generation from LSLB). Additionally, the lengths of the other bronchi that were analysed did not exhibit a decreasing trend. Consequently, our data did not indicate the occurrence of node retraction.

The present analysis indicates that the LSLB evidently bifurcated through dipodial branching. In the current investigation, this was the sole bronchus that was segmented by dipodial branching. The mouse lungs lack a bronchus that anatomically corresponds to the superior division of the bronchus and LB, as mice have only one lobe in the left lung. In contrast, the left lung in humans is composed of two lobes, with the left superior lobe being generally larger than the right superior lobe. The right middle lobe and lingula are frequently the sites of chronic inflammatory disorders, including middle lobe syndrome and lingular syndrome. Consequently, the left superior bronchus appears to be a unique branch from the perspective of clinical significance. The LSLB's characteristic branching mode may be indicative of an anatomically distinctive structure that is exclusive to human lungs.

There were certain constraints associated with this investigation. Initially, the categorization of the branching mode was influenced by individual differences, as the current study employed the minimum and maximum lengths for categorization. Secondly, we did not further divide the branching modes into additional categories; however, a variety of branching modes have been reported. The branching modes could be further subdivided into more than two modes by incorporating morphometric data, such as angles or widths.

CONCLUSION

The branching morphogenesis of the proximal bronchus was examined in the current study by measuring its length. Monopodial branching was observed in nearly all proximal bronchi, with the exception of the LSLB, as evidenced by a morphometric analysis. In order to clarify the branching morphogenesis, future analyses of parameters other than length, such as angles or widths, are required.

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