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Fetus Cardiovasculler

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A B S T R A C T

Formation of the human heart involves complex biological signals, interactions, specification of myocardial progenitor cells, and heart tube looping. To facilitate survival in the hy poxemic intrauterine environment, the fetus possesses structural, physiological, and functional cardiovascular adaptations that are fundamentally different from the neonate. The fetal circulation is considered to anatomical and biochemical changes in the cardiovascular system. This review article describes key cardiac progenitors involved in embryonic heart development; the cellular, physiological, and anatomical changes during the transition from fetal to neonatal circulation.

I. INTRODUCTION

The human heart is one of the first organs to form and function during embryogenesis (Timor-Tritsch et al, 2012, Fylstra DL, 2002). By the end of gestational week 3, passive oxygen diffusion becomes insufficient to support metabolism of the developing embryo (Marchiolé P et al, 2004, Jurkovic D et al, 2003) and thus the fetal heart becomes vital for oxygen and nutrient distribution. The initiation of the first heart beat via the primitive heart tube begins at gestational day 22, followed by active fetal blood circulation by the end of week 4 (Timor-Tritsch et al, 2012, Marchiolé P et al, 2004, Jurkovic D et al, 2003).

The start of early heart development involves several types of progenitor cells that are derived from the mesoderm, proepicardium, and neural crest. This eventually leads to the formation of the 4 chambered heart by gestational week 7 via heart looping and complex cellular interactions in utero (Fylstra DL, 2002). Intrauterine fetal life is sustained in a secure, and hypoxemic environment that is dependent on the mother's placenta for nutrition, respiration, waste elimination, and metabolism (Gonzalez, Tulandi 2017). To facilitate survival in the hypoxemic intrauterine environment, the fetus possesses structural, physiological, and functional cardiovascular adaptations that are fundamentally different from the neonate (Marchiolé P et al, 2004), (Seow KM et al, 2004). At birth, upon separation from the pla cental circulation, the neonatal cardiovascular system takes over responsibility of vital processes (Gonzalez, Tulandi 2017).

This review article highlights important fetal cardiac development, cardiovascular system cellular, physiological, and anatomical from fetal to neonatal circulation, as well as caused by congenital cardiac malformations and pregnancy complications.

Early Cardiogenesis

Transcription factors mesoderm posterior 1 and 2 (MESP1/2) are the earliest markers of cardiovascular specification and are expressed at the start of gastrulation (Jachymski et al, 2020), (Jabeen , Karuppaswamy, 2018). MESP1 represses pluripotent inducing genes and drives expression of cardiac transcription factors (Grechukhina et al 2018). As cardiac precursors migrate away from the primitive streak to form the cardiac crescent, *MESP1/2* is down regulated while activating other transcription factor networks that drive cardiac specifica tion. Early heart development involves myocardial progenitor cells, including first heart field (FHF) and second heart field (SHF) progenitor cells, as well as proepicardial progenitor cells derived from the lateral plate mesoderm and ectoderm derived cranial neural crest cells (Fig.1)These cells emerge via the interaction of inductive and inhibitory signals from the germ layers (endoderm, mesoderm, and ectoderm) during gastrulation (Fylstra , 2002), (Harb et al, 2018, Birch et al, 2016).

Molecular signals include cardiac differentiation inhibitors (i.e., wingles integrated, Wnt) and cardiac differentiation inducers (i.e., fibroblast growth factor, FGF and bone morphogenetic proteins, BMPs) (Birch PK et al, 2016), (Timor-Tritsch et al, 2014). Disruption in Wnt/β-catenin signaling in endoderm via deletionof *β-catenin* results in the formation of ectopic cardiac tissue in the overlying mesoderm(Timor-Tritsch et al, 2014).

Formation of Cardiac Chambers: Heart Tube Formation and Looping

The specification and differentiation of progenitor cells via specific heart fields are critical for embryonic heart development (Fylstra , 2002 , Calì G et al 2018). During the second week of human gestation, the cardiac mesodermal cells migrate to ward the anterior direction of the embryo to form the 2 major cardiac progenitor pools: the earliest cells to express MESP1 form the FHF or cardiac crescent and the later wave of MESP 1 produces cells that form the SHF (located posterior to the crescent; Fig.1 (Timor-Tritsch et al , 2012, Birch et al, 2016, Calì G et al 2018, Gao et al, 2016).Both FHF and SHF express specific transcription factorsand are the main reservoirs for cardiomyocytes, where mononucleated cardiomyocytes undergo hyperplasia in

order to increase cell number for cardiac growth (Timor-Tritsch et al, 2012, Fylstra , 2002, Birch et al, 2016, Calì G et al 2018, Armstrong et al, 2000, Christoffels et al, 2010).

The specification of cardiac chamber morphogenesis is modulated by several transcription factors, including T-box transcription factors TBX2, TBX3, TBX5, and TBX20; as well as NKX2–5, GATA4, and HAND1 (Jabeen , Karuppaswamy , 2018).

GATA 4 and NKX2-5 in combination with TBX5 and TBX20 promote myocardial specification via the expression of chamber myocardium specific genes including induction of atrial natriuretic factor, gap junction protein connexins 40/43, and transcriptional repressor ID2, which improves contractibility and patterning of the right ventricular (RV) and left ventricular (LV) bundle branches (Christoffels et al, 2010, Singh et al, 2005). BMP induced BX2/3 expression is involved in non chamber myocardial specification including the atrioventricular canal, outflow and inflow tract (Gittenbergerde et al, 2014). *TBX20*, an inhibitor of BMP induced TBX2/3 activation, is broadly expressed throughout the linear heart tube to ensure chamber myocardium specification. Deletion of *TBX20* results in defects in chamber development (Gittenbergerde et al, 2013). Furthermore, disturbance of morphogenetic transcription and growth factors including TBX1, TBX5, GATA4, and BMP4 within the SHF derived cell populations may result in a spectrum of ventricular septal defects at the outflow tract (Latham et al, 2019). Ventricular septal defects are characterized by membranous ventricular septum via the fusion of the endocardial outflow tract and atrio ventricular canal, which allows blood to pass form the left to right side of the heart (Yang et al, 2013). If significant in size and unrepaired postnatally, they can result in elevation in pulmonary vascular resistance (PVR), pulmonary arterial pressure, hypoxia, and cyanosis (Lin et al, 2012).

The SHF of the human embryo shows a dynamic spatiotemporal distribution pattern (Auman et al, 2007). During the third week, the FHF fuses at the midline to form the primitive heart tube, which starts to beat at around embryonic day. (Lin et al 2012) and eventually gives rise to the LV and parts of the right and left atria (Fylstra , 2002, Birch et al, 2016, Gao et al, 2016), Armstrong et al, 2000) .

Blood flow and contraction causes peristaltic pumping motion in the linear heart tube, which may contribute to the ballooning process since endocardial and myocardial cells alter their shape, size, and proliferation in response to mechanical stress (Moorman et al, 2003, Samsa et al, 2003). Subsequently, during week 4, the heart tube undergoes righ tward looping, with its posterior region moving anteriorly. SHF progenitors, located behind the primary heart tube within the pharyngeal mesoderm, migrate toward the primitive and looping heart tube, contributing to the RV, parts of the atria, septum and outflow tract, and later to the base of the aorta and pulmonary trunk (Birch et al, 2016, Auman et al, 2007). The cells from the venous poles contribute to the base of the superior and inferior vena cava (SVC and IVC, respectively) (Birch et al, 2016).]

Cardiac trabeculation occurs after the cardiac looping, it promotes the formation of luminal projections (trabeculae), which consist of myocardial cells enclosed by the endocardial layer (Moorman et al, 2003).Trabeculation and subsequent compaction of the ventricular myocardium facilitates septation, increases cardiac output, contractility and conductivity, and helps establish the coronary circulation system in the developing heart (Moorman et al, 2003), Escot et al, 2013). *NOTCH1* regulates trabecular growth via promoting endothelial growth factor neuregulin-1 activity through endocardial Ephrin B2 (Zhou et al, 2008).

Formation of the Epicardium, Heart Valves, and Parasympathetic Innervation

The embryonic pro-epicardial progenitor cells located at the celomic mesenchyme of the septum transversum will differentiate into cardiac fibroblasts, coronary vasculature, and a small number of cardiomyocytes, which eventually form the outer lining of the (epicardium) (Timor-Tritsch et al, 2012 , Birch et al, 2016, Keyte, Hutson, 2012).The fourth progenitor population

involved in hu- man embryonic cardiogenesis consists of the cranial neural crest cells, which migrate in from the dorsal neural tube through the pharyngeal arches via stromal cell derived factor 1 as a chemotactic agent (Hasten et al 2018). The neural crest cells are involved in septation of the outflowtract and the formation of heart valves, with *NOTCH1* contributing to heart valve formation.

Several gene mutations in *NOTCH1* have now been reported in the human population to be associated with bicuspid aortic valve (Yang et al 2013). Neural crest cells also give rise to smooth muscle cells within aortic and pulmonary arteries, along with the full autonomic and sensory innervation of the heart (Birch et al, 2016). Anomalies in the cardiac neural crest are responsible for a multitude of human cardio-cranio-facial defects, such as DiGeorge syndrome, which is associated with *TBX1* deletion (Fylstra , 2002, Birch et al, 2016, Calì et al 2018). Through the looping process, complex interactions of FHF and SHF progenitors, as well as pro-epicardial and cranial neural crest cells, the fetal heart is septated into 4 defined cardiac chambers, which connect to the aorta and pulmonary trunk around gestational week 7 (Fylstra , 2002, Birch et al, 2016, Calì et al 2018).

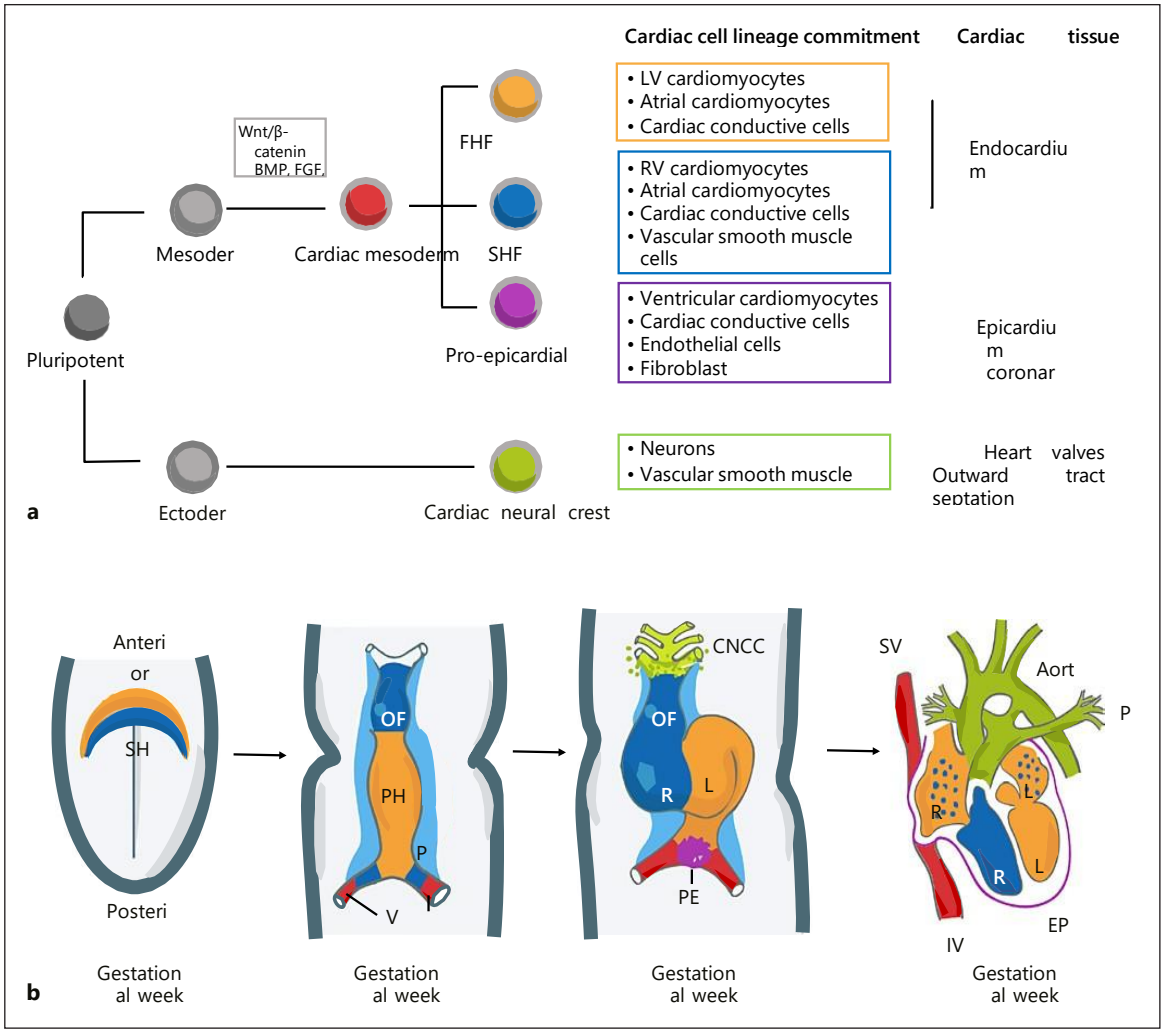

Fig.1. Early cardiac development (Kiserud, 2005).

a. Cardiac cell lineage and specification during development demonstrating the commitment of pluripotent cells toward mature cardiac cell types within the heart development.

b Schematic of cardiac morphogenesis in humans.

At the second week of gestation, the cardiogenic mesodermal cells migrate toward the anterior side of the embryo to form the FHF or cardiac crescent and SHF that are specified to form specific segments of the PHT, which is patterned along the antero posterior axis to form the various regions and chambers of the looped and mature heart during weeks 3 and 4. The FHF gives rise to the beating PHT and will eventually give rise to the LV and parts of the right and left atria (RA and LA, respectively). The SHF, located behind the PHT and within the pharyngeal mesoderm by gestational week 3, will contribute to the formation of the RV, parts of the atria and outflow tract, and later to the base of the aorta and pulmonary artery.

At gestational week 3, the cells at the venous pole contribute to the formation of the superior and inferior vena cavas (IVC, respectively). By gestational week 4, the cardiac neural crest cells migrate in from the dorsal neural tube, forming smooth muscle cells within the aortic and pulmonary arteries. In addition, the proepicardial organ formed by the proepicardial progenitor cell clusters later contributes to the formation of the epicardium. The 4 chambers form by the end of week 7. Wnt, Wingles inte- grated; FGF, fibroblast growth factor; BMP, bone morphogenetic proteins; FHF, first heart field; SHF, second heart field; OFT, out- flow tract; PHT, primary heart tube; PM, pharyngeal mesoderm; VP, venous pole; CNCCs, cardiac neural crest cells; LV, left ven- tricle; RV, right ventricle; PEO, proepicardial organ; SVC, supe- rior vena cavas; IVC, inferior vena cavas; EPC, epicardium; and PA, pulmonary artery.

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Anomalies in the cardiac neural crest are responsiblefor a multitude of human cardio-cranio-facial defects, such as DiGeorge syndrome, which is associated with *TBX1* deletion (Blackburn, 2014). Through the looping process, complex interactions of FHF and SHF progenitors, as well as pro-epicardial and cranial neural crest cells, the fetal heart is septated into 4 defined cardiac chambers, which connect to the aorta and pulmonary trunk around gestational week 7 .(Birch et al, 2016, Calì et al 2018).

The Fetal Cardiovascular System

The fetal cardiovascular system is adapted biochemically and structurally to ensure that the highly oxygenated blood is delivered preferentially from the placenta to the brain and the heart while being diverted away from the lungs. The combination of the following contributes to the maintenance of the fetal cardiovascular system: (i) biochemical factors, including vasoregulatory agents such as prostaglandins and endothelin-1 and (ii) anatomical adaptations, such as the presence of 4 shunts: the placenta, ductus venosus (DV), ductus arteriosus (DA), and foramen ovale (FO; Fig.2) (Gonzalez, Tulandi 2017).

Fetal Structural Adaptations: The Four Shunts in Fetal Circulation

By the 10th week of gestation, the fetal circulation has transitioned from passive gas exchange by both the yolksac and the placenta to being placenta dominant (Fig.2)The placenta is not only the source of nutrition but also an organ of waste elimination for the fetus; the supply of nutrients, as well as the exchange of oxygen and waste products, takes place in the intervillous spac. It is a low resistance vascular bed, which promotes the fetal to maternal exchange of deoxygenated blood under low pressure (Marchiolé et al, 2004, Gupta , Paria, 2016). Despite the low partial pressure of oxygen in the placenta, oxygen delivery to fetal tissues remains adequate due to the combined high ventricular output and the presence of fetal hemoglobin, which has a higher oxygen affinity than adult hemoglobin (Gupta, 2016, Sharma, et al 2014, Edelstone et al, 1978).Following oxygenation in the intervillous spaces, relatively oxygenated fetal blood is carried by the umbilicalvein to the liver (Jurkovic et al, 2003), (Reynolds , 2013). The DV allows 50–60% of umbilical vein blood to by pass the hepatic circulation andenter the IVC, mixing with desaturated IVC blood (Gonzalez, Tulandi 2017).The remainder of blood perfuses the liver, ultimately merging with desaturated blood from the lower part ofthe body via the IVC to enter the right atrium (Gonzalez, Tulandi 2017). In the right atrium, blood is diverted into 2 streams, with more than half traversing the FO in the inter atrial septum to enter the left atrium (Gao et al, 2016, Gupta , 2016,(Sharma , et al 2014, Artman et al, 2002). This oxygen saturated blood then passes through the LV and mixes withthe pulmonary venous return to be pumped through the ascending aorta toward the carotid and coronary arteries (Gao et al, 2016, Gupta , 2016, Schneider, 2006). The remainder of IVC blood flow mixes with desaturated blood from the superior vena cava, which first enters the RV through the tricuspid valve and, subsequently, the pulmonary artery .The high PVR results in the majority of blood that leaves the RV being preferentially shunted through the DA, by passing the pulmonary circulation and going directly into the descending aorta. As a result, only 8–10% of total cardiacoutput passes through the high resistance pulmonary circulation (Gupta , Paria, 2016), Approximately 40–60% of blood that enters the descending aorta either supplies theumbilical artery to the lower limbs or is reoxygenated at the placenta (Reynolds, 2013).

Fetal Combined Ventricular Output and Heart Rate

Normal fetal heart rate ranges from 110 to 160 beats per minute (Table) (Kiserud, 2005), with the low resistance placental bed providing a low systemic vascular resistance (SVR) and absorbing over 40% of the combined cardiac outputfrom both ventricles. Increased PVR combined with low SVR results in the right to left shunting of blood through the FO and the patent ductus arteriosus (PDA), with the RV accounting for two-thirds of cardiac output perfusing the lower half of the body and placenta. LV out-put is directed toward the coronary and carotid arteries, supplying the heart muscle wall and brain ((Sharma A, et al 2014), . The amount of blood entering the pulmonary circulation varies during pregnancy, increasing from just over 10% of the combined cardiac output at mid-gestation to around 25% by 30 weeks' gestation [(Jurkovic D et al, 2003)]. Perfusion rate offetal tissues is higher than in the adult, with normal rang-es of 470–500 mL/kg/min measured by Doppler ultrasound (Table) (Kiserud, 2005).

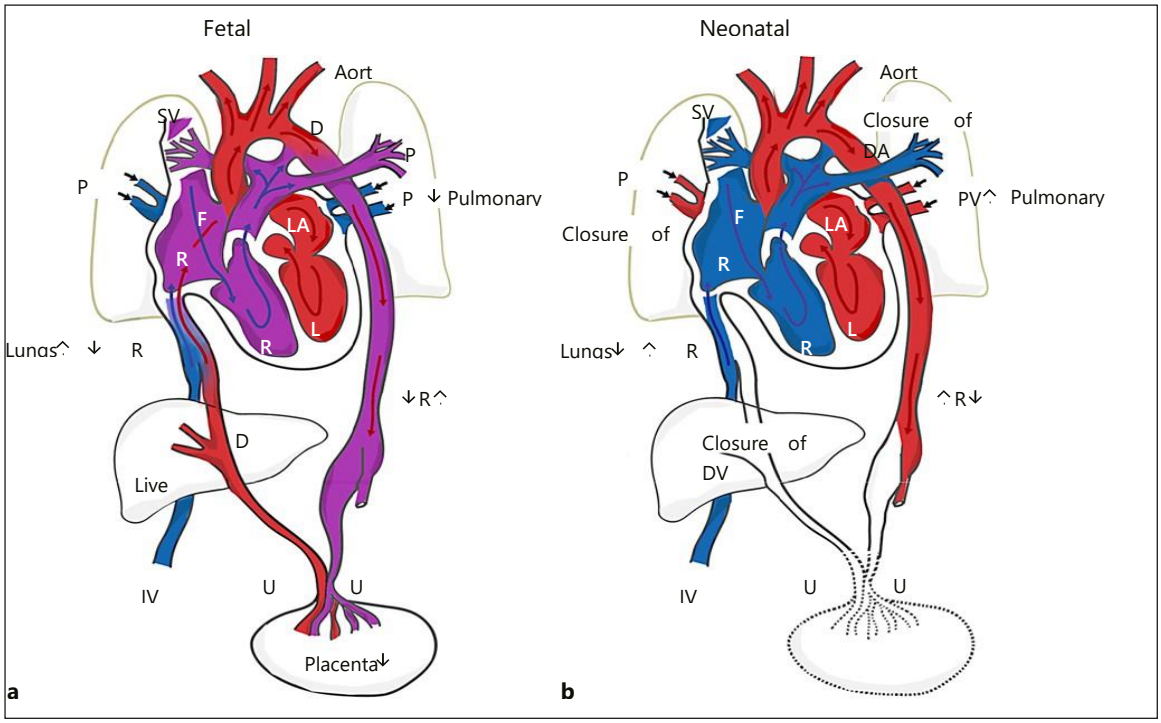

Fig. 2. Schematic of normal fetal and neonatal cardiovascular circulation.(Edelstone et al, 1978)

a . During fetal development, oxygenated and nutrient rich fetal blood from the placenta passes to the fetus via the umbilical vein.

Approximately half of this blood bypasses the liver via the DV and enters the IVC. The remainder enters the portal vein to supply the liver with nutrients and oxygen. Blood entering the RA from the IVC bypasses the RV as the lungs are not yet functioning, and then enters the LA via the FO. Blood from the SVC enters the RA, passes to the RV, and moves into the PA trunk. Most of this blood enters the aorta via the DA, a right to left shunt. The partially oxygenated blood in the aorta returns to the placenta via the paired UA that arise from the internal iliac arteries.

b. Under normal physiological conditions, when pulmonary respiration begins at birth, pulmonary blood pressure falls, causing blood from the main PA trunk to enter the left PA and right PA, become oxygenated at the lungs, and then return to the LA via the PV.
The FO and DA close, eliminating the fetal right to left shunts. The pulmonary and systemic circulations in the heart are now separate. As the infant is separated from the placenta, the UAs occlude (except for the proximal portions), along with the umbilical vein and DV. Blood to be metabolized now passes through the liver. DV, ductus venosus; UV, umbilical vein; IVC, inferior vena cava; RA, right atrium; RV, right ventricle; LA, left atrium; FO, foramen ovale; SVC, superior vena cava; PA, pulmonary artery; DA, ductus arteriosus; UA, umbilical arteries; PV, pulmonary veins.

Table. Differences between fetal and postnatal circulations((Kiserud, 2005))

Circulation	Circuits	Site of gas exchange	Shunts	Perfusion rate, mL/kg/min	Heart rate (beats per min)	Vascular resistance
Fetal	Parallel	Placenta	DV, DA, FO	470–500	110–160	Pulmonary >systemic
Neonatal	Series	Lungs	Closure of shunts: DV→Ligamentum venosum DA → Ligamentum arteriosumFO→ Fossa ovalis	200	100–120	Systemic >pulmonary

DV, ductus venosus; DA, ductus arteriosum; FO, foramen ovale.

Conclusion

The development of the heart begins as early as the third week of gestation with the 4-chamber fetal heart formed by gestational week 7. It involves complex biochemical signals, interactions, and specification of myocardial progenitor cells and heart tube looping. The fetal and neonatal circulation is considered to be a period of physiological, anatomical, and biochemical changes in the cardiovascular system. Identifying abnormalities in early cardiogenesis and the cardiovascular physiology from fetal life is essential for the immediate and long term cardiovascular health risk.

Disclosure Statement

The authors declare no conflicts of interest.

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