Evolutionary Changes of the Cardiovascular System
Initiated by Reduced Atmospheric O_2 Gave Rise to Mammalian and Avian Endothermy

Gerald Soslau*
Department of Biochemistry and Molecular Biology, Drexel University College of Medicine, 245 N 15th Street, Philadelphia, PA 19102, USA

*Correspondence should be addressed to Gerald Soslau; gsoslau@drexel.edu

Received date: July 30, 2021, Accepted date: August 19, 2021

Copyright: ©2021 Soslau G. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract
The evolution from ectotherm to endotherm with all the attendant genetic and structural modifications was the single most important biological event for the establishment of the hominoid species. A previous publication hypothesized that the appearance of small, enucleated red blood cells (RBCs) and platelets in mammals, reduced RBC size in birds, increased vascular density in all tissues, and the evolution of the four-chambered heart were required for the evolution of avian and mammalian endothermy. The genetic and structural changes in birds and mammals were initiated by the selective pressure of low atmospheric oxygen during the Permian period and ultimately led to endothermy [1]. The establishment of endothermy in mammals and birds afforded animals a more efficient cardiovascular system to exchange O_2 for metabolically produced CO_2 in their tissues than occurs in ectotherms. This permitted mammals to maintain: their body temperature in expanded environmental niches; a constant energy production with optimized enzyme activity that could facilitate the flight-or-fight response; lactation for off-spring; and increased brain size, to name a few advantages. A better understanding of the molecular events that led to endothermy would add much to our understanding of many diseased states and would facilitate the development of targeted drugs for their treatment.

Introduction
This commentary will address the salient points explored in a previous publication on the role of the red blood cell and platelet in the evolution of mammalian and avian endothermy [1], include additional concepts associated with the evolution of endothermy, and finally address future directions that may be followed in this area of research. The most simplistic definition of the terms endothermic and ectothermic is the former refers to warm-blooded animals that maintain their body temperature by endogenous mechanisms while the latter refers to cold-blooded animals that require external sources of heat to warm their bodies. In actuality the ability to maintain body heat is more complex for many animals categorized by these terms since some large-bodied ectotherms can maintain body temperatures by internal mechanisms and some endotherms do not maintain body temperature at selective times, such as when hibernating [2-7].

It was hypothesized that environmental pressures during the Permian/Triassic period when there was a dramatic drop in atmospheric O_2 selected for vertebrates with genetic mutations that afforded the animal more efficient pathways to transport O_2 to their tissues. Over millennia multiple mutations resulted in genetic and structural changes in the cardiovascular system and the cells within their blood. Structural changes included: the transition to a four-chamber heart that permitted the formation of high-pressure systemic and low-pressure pulmonary circulation [8]; greatly increased density of capillary networks and arterioles to allow for more efficient gas exchange [9]; a pulmonary/systemic differential of blood flow/pressure to enhance gas exchange in lungs; reduced red blood cell size with greater cell surface area/cell to enhance gas exchange at the tissue level, and in the case of mammals the enucleation of both red blood cells and platelets. The initial changes would have been directed by genetic mutations of genes in an ancestor common to
Soslau G. Evolutionary Changes of the Cardiovascular System Initiated by Reduced Atmospheric O₂ Gave Rise to Mammalian and Avian Endothermy. J Clin Haematol. 2021; 2(3): 101-105.

both mammals and avian, however, the final switch to endothermy in avian lagged behind that for mammals.

While there are many different models proposed for the evolution of endothermy [10,5,11,12], some of which we will discuss herein, “recent evidence suggests that the delivery of oxygen by the cardiovascular system represents the fundamental rate limitation to maximal oxygen consumption and aerobic metabolism in all vertebrates” [13]. That this process is so fundamental to life and that mammalian and avian species have an enhanced capacity to deliver oxygen to their tissues more efficiently than ectotherms is reason to believe that the oxygen-depravation during the Permian/Triassic period was in fact a major driving force for the evolution of endothermy in mammalian and avian species.

Further support for the hypothesis that red blood cell mutations were critical for the evolution from ectotherm to endotherm is derived from studies of mammalian embryos. Mouse embryo erythroid production begins in the yolk sac yielding large, nucleated RBCs, primitive erythrocytes (EryP), that enter the embryo circulation prior to reduction in cell size and enucleation [14,15]. The mouse embryo begins synthesizing EryPs at day 7.25 and by day 10.5 have established a functional circulatory system. These nucleated RBCs transport oxygen and it is only by day 12.5 to 16.5 that the EryP undergo final maturation steps and extrude their nuclei [16]. Darwin recognized in the mid-1800’s that embryonic structures revealed genetic linkages between species that would not have been surmised from comparative studies of the mature species. These EryP cells have all the characteristics of the large, functional, nucleated RBCs present in extant endotherms and likely found in primordial ectotherms from which endotherms evolved.

Studies also indicate that the embryonic progenitor of primitive RBCs (hemangiblast) is bipotent giving rise to megakaryocytes and primitive RBCs [17] reflecting an ancient pathway that evolved into the adult endothermic bipotential precursor cell for megakaryocytes and RBCs (megakaryocyte-erythroid progenitor [MEP]) in both mammals and birds. The linkage of bipotent precursor cells for megakaryocyte and RBC production would support a linked role for the two cell types in the evolution of endothermic animals from ectothermic animals. The importance of platelets in the evolution of endotherms is not just relegated to their role in hemostasis and cardiovascular homeostasis but also to the critical role they play in separating the blood and the lymphatic vasculatures during embryonic development [18].

Interestingly, cultured EryP progenitor numbers increased in both number and size in response to low O₂ conditions and aerobically metabolized glucose to lactate in lieu of the more energy efficient mitochondrial oxidative-phosphorylation (Krebs cycle/cytochrome) pathway [14], perhaps reflecting an early stress response to low O₂ in the Permian/Triassic period. It is also significant to note that the embryonic forms of hemoglobin subunits found in the human embryo, zeta-globin and epsilon-globin have the same (epsilon) or greater (zeta) capacity for O₂ binding in transgenic mice carrying the human hemoglobin genes [19]. Thus, ancient forms of the hemoglobin subunits, if one accepts embryonic proteins that are replaced by adult forms represent earlier life forms, have the same or greater capacity to transport O₂ to tissues in exchange for CO₂. This would have benefited ancestors of early mammals during the evolution from low density capillary beds found in ectotherms to more dense vascular tissues found in endotherms [9].

A recent report again lends further support for increased O₂ utilization by tissues as facilitating the evolution of endothermy [20]. This group presented evidence for mutations in the RNA splicing mechanism of a Krebs cycle enzyme subunit in early terrestrial ectotherms that gave rise to a Ca²⁺-dependent form of the enzyme that regulates the generation of NADH required to generate ATP under aerobic conditions through the oxidative/phosphorylation pathway in mitochondria. They hypothesized that this altered splice choice “facilitated evolution of endothermy by optimizing the aerobic scope in target tissue” [20]. This optimization of aerobic metabolism would go hand-in-hand with the enhanced delivery of O₂ to tissues by smaller, enucleated RBCs with greater O₂ delivery capacity to endotherms’ tissues through more dense vascular beds than found in ectotherms [1].

In a quantitative analysis of vascular density, as determined in histological sections of bone derived from fossil eosauropterygians and samples from extant comparative taxa, it was concluded that plesiosaurs had bone growth rates and resting metabolic rates that were very similar to those of extant birds [21]. Based upon these observations the group suggested that plesiosaurs were endothermic. They further state “it is widely agreed that endothermy evolved several times independently. Among recent species, true endothermy, however, is only present in mammals and birds” [21]. In actuality it is not clear just how widely the concept that endothermy “evolved several times independently” is accepted.

Wu et al. [22] state that endothermy has evolved independently at least eight times in vertebrates. They found that mutations had occurred in proteins related to heat production in two “endothermic” teleost lineages, billfishes, and tunas. As stated earlier, several large-bodied ectothermic vertebrates can indeed regulate their body temperature in cold conditions, but this is a phenomenon of a few species within a Class of animals and not “true endothermy” [21,23]. The use of the term “evolved independently” is also difficult to imagine
when considering the large number of mutations and structural modifications that were required to achieve true endothermy in birds and mammals.

Wu and Wang [24] listed many of the functionally shared characteristics by birds and mammals that required evolutionary mutations and structural changes: “such as enhanced hearing, vocal communications, endothermy, insulation, shivering, respiratory turbinals, high basal metabolism, grinding, sustained activity, four-chambered heart, and intensive parental care.” This evolutionary process occurred with parallel characteristics in both birds and mammals even though there was a lag time for birds. It is hard to imagine that all of these genetic alterations occurred independently in birds and mammals but would rather indicate that an ancient ancestor to both birds and mammals, such as Archosauromorpha, or some other unknown common ancestor, contained the required genetic information that when exposed to the proper stimulants would evolve with parallel outcomes.

The significance of the switch from ectotherm to endotherm cannot be overstated for the wellbeing and adaptability of endotherms to life on Earth, especially in geographic regions with large seasonal temperature changes. Several different theories have been proposed through the years to explain the evolutionary change to endotherms. None of these proposals are mutually exclusive and in reality, the true pressure for change may in fact be a composite of two or all of these hypotheses.

A highly touted theory for the evolution of endothermy has been based upon the aerobic capacity model that assumes a positive phenotypic correlation between basal metabolic rate (BMR) and the maximum metabolic rate (MMR). The model proposed that selective pressures for endothermy evolved in animals with the capacity to increase their MMR. While there may be some component of this model truly associated with the evolution of endothermy, several studies cast doubt that it was the driving force since there is little data to support a correlation between BMR and MMR [5,25,26]. However, it is clear that the increased ability to transport oxygen to the tissues [1] would allow animals to increase their MMR.

Another proposal was based upon a selective response to parental care, where endothermy allowed parents to control incubation temperatures. It was posited that the ability to sustain vigorous exercise was also an effect of selection for parental care which so often is associated with vigorous activity [10]. The proposal that parental care was a selective effector in the evolution of endothermy was also linked to the aerobic capacity model where the evolution of a high metabolic rate would accommodate the evolution of intensive parental care [11].

Other theories have been proffered as the driving force in the evolution of endothermy. One is based upon climate change, especially exposure to cold, that resulted in an increase in energy turnover/metabolism leading to the endothermic state [12]. Finally, it has been proposed that a reduction in body size contributed to the evolutionary pathway to endothermy [23,27] with the hypothesis that genetic mutations of genes got activated during ontogeny and regulated growth resulting in early growth stop [27].

Lovegrove [3] proposed a three-phase model for the evolution of endothermy that incorporates all of the above hypotheses. In the first phase during the Permian period, with a low O₂ environment, animals with the ability to increase their metabolism and body temperature (enhanced O₂ delivery to tissues as previously proposed [1]), would have had selective advantages along with enhanced embryo development (parental care). The second phase entailed the extreme reduction in body size, surface structures for insulation (fur and feathers), increased brain size, and thermoregulatory control. The last phase involved structural changes such as muscle-powered flapping flight in birds, perhaps the development of the four-chambered heart, and climate adaptation. Wu and Wang [24] proposed an integrated schematic for the evolution of endothermy that included everything in Lovegrove’s hypothesis but added increased oxygen supply and nocturnality. They hypothesized that nocturnal behavior in ancestral birds and mammals subjected these animals to cold evening temperatures that was a selective pressure to establish endothermic characteristics for vigorous nighttime activities.

Another genetic modification occurred some 500 million years ago that did not selectively drive the evolution of endothermy but eventually contributed to critical anatomic structures in endotherms, that of the emergence of collagen I in vertebrates. Collagen I along with collagen I-binding integrins “resulted in the dramatic stiffness of the extracellular environment” affording vertebrates the opportunity to generate new structures such as the development of the blood-brain barrier, the mammalian placenta and trophoblast invasion of the uterine wall during embryo implantation [28].

This latter finding is an example of the scientific value of understanding the molecular changes in the evolution of endothermy. The identification of genetic mutations that led to the evolution of endothermy would facilitate the unraveling of the etiology of some diseases related to the cardiovascular system and the unique cell types within it, along with the development of targeted drugs for treatment of these diseases. Diseases that result from developmental abnormalities of platelets and RBCs would be of particular interest such as: essential thrombocytopenia [29]; thrombocytopenia [30]; dyserythropoietic anemia [31]; disorders of the erythrocyte membrane [32], and; the chromosome 11 defect in Jacobsen syndrome with an associated platelet defect [33]. In addition to these
diseases of blood cells, defects in the development of the four-chambered heart could be approached using the avian embryo as a model as recently described [34]. Knowledge of specific genes that are altered in the diseased state could also lead to cures using the CRISPR-Cas9 genome editing methodology. New, innovative methodologies that can sequence DNA in selected embryonic cells, such as the fetal nucleated RBC [35], or the transcriptome for a single hematopoietic lineage of the embryo [36] should go a long way to expanding our knowledge of molecular events associated with the evolution of endothermy.

References

1. Soslau G. The role of the red blood cell and platelet in the evolution of mammalian and avian endothermy. Journal of Experimental Zoology Part B: Molecular and Developmental Evolution. 2020 Mar;334(2):113-27.

2. Lovegrove BG. The evolution of endothermy in Cenozoic mammals: a plesiomorphic-apomorphic continuum. Biological Reviews. 2012 Feb;87(1):128-62.

3. Lovegrove BG. A phenology of the evolution of endothermy in birds and mammals. Biological Reviews. 2017 May;92(2):1213-40.

4. Porter WR, Witmer LM. Vascular patterns in iguanas and other squamates: blood vessels and sites of thermal exchange. PLOS One. 2015 Oct 14;10(10):e0139215.

5. Hayes JP, Garland Jr T. The evolution of endothermy: testing the aerobic capacity model. Evolution. 1995 Oct;49(5):836-47.

6. Paladino FV, O’Connor MP, Spotila JR. Metabolism of leatherback turtles, gigantothermy, and thermoregulation of dinosaurs. Nature. 1990 Apr;344(6269):858-60.

7. Spotila JR, Lommen PW, Bakken GS, Gates DM. A mathematical model for body temperatures of large reptiles: implications for dinosaur ecology. The American Naturalist. 1973 May 1;107(955):391-404.

8. Poelmann RE, Gittenberger-de Groot AC. Development and evolution of the metazoan heart. Developmental Dynamics. 2019 Aug;248(8):634-56.

9. Pough FH. Blood oxygen transport and delivery in reptiles. American Zoologist. 1980 Feb 1;20(1):173-85.

10. Farmer CG. Parental care: the key to understanding endothermy and other convergent features in birds and mammals. The American Naturalist. 2000 Mar;155(3):326-34.

11. Koteja P. The evolution of concepts on the evolution of endothermy in birds and mammals. Physiological and Biochemical Zoology. 2004 Nov;77(6):1043-50.

12. Pörtner HO. Climate variability and the energetic pathways of evolution: the origin of endothermy in mammals and birds. Physiological and Biochemical Zoology. 2004 Nov;77(6):959-81.

13. Hedrick MS, Hillman SS. What drove the evolution of endothermy? Journal of Experimental Biology. 2016 Feb;219(3):300-1.

14. Baron MH, Isern J, Fraser ST. The embryonic origins of erythropoiesis in mammals. Blood, The Journal of the American Society of Hematology. 2012 May 24;119(21):4828-37.

15. Barminko J, Reinholt B, Baron MH. Development and differentiation of the erythroid lineage in mammals. Developmental & Comparative Immunology. 2016 May 1;58:18-29.

16. Palis J. Hematopoietic stem cell-independent hematopoiesis: emergence of erythroid, megakaryocyte, and myeloid potential in the mammalian embryo. FEBS letters. 2016 Nov 1;590(22):3965-74.

17. Tober J, Koniski A, McGrath KE, Vemisetti R, Emerson R, de Mesy-Bentley KK, et al. The megakaryocyte lineage originates from hemangioblast precursors and is an integral component both of primitive and of definitive hematopoiesis. Blood. 2007 Feb 15;109(4):1433-41.

18. Carramolino L, Fuentes J, Garcia-Andres C, Azcoitia V, Riethmacher D, Torres M. Platelets play an essential role in separating the blood and lymphatic vasculatures during embryonic angiogenesis. Circulation Research. 2010 Apr 16;106(7):1197-201.

19. He Z, Lian L, Asakura T, Russell JE. Functional effects of replacing human α-and β-globins with their embryonic globin homologues in defined haemoglobin heterotetramers. British Journal of Haematology. 2000 Jun;109(4):882-90.

20. Královičová J, Borovská I, Pengelly R, Lee E, Abaffy P, Šindelka R, et al. Restriction of an intron size en route to endothermy. Nucleic Acids Research. 2021 Mar 18;49(5):2460-87.

21. Fleischle CV, Wintrich T, Sander PM. Quantitative histological models suggest endothermy in plesiosaurs. Peer J. 2018 Jun 6;6:e4955.

22. Wu B, Feng C, Zhu C, Xu W, Yuan Y, Hu M, et al. The Genomes of Two Billfishes Provide Insights into the Evolution of Endothermy in Teleosts. Molecular Biology and Evolution. 2021 Jun;38(6):2413-27.
23. Rezende EL, Bacigalupe LD, Nespolo RF, Bozinovic F. Shrinking dinosaurs and the evolution of endothermy in birds. Science Advances. 2020 Jan 1;6(1):eaaw4486.

24. Wu Y, Wang H. Convergent evolution of bird-mammal shared characteristics for adapting to nocturnality. Proceedings of the Royal Society B. 2019 Feb 27;286(1897):20182185.

25. Swanson DL, Thomas NE, Liknes ET, Cooper SJ. Intraspecific correlations of basal and maximal metabolic rates in birds and the aerobic capacity model for the evolution of endothermy. PLOS One. 2012 Mar 27;7(3):e34271.

26. Nespolo RF, Roff DA. Testing the aerobic model for the evolution of endothermy: implications of using present correlations to infer past evolution. The American Naturalist. 2014 Jan 1;183(1):74-83.

27. Werner J, Griebeler EM. Was endothermy in amniotes induced by an early stop in growth during ontogeny? The Science of Nature. 2017 Dec;104(11):1-8.

28. Tang VW. Collagen, stiffness, and adhesion: the evolutionary basis of vertebrate mechanobiology. Molecular Biology of the Cell. 2020 Aug 1;31(17):1823-34.

29. Tefferi A, Pardanani A. Essential thrombocytopenia. New England Journal of Medicine. 2019 Nov 28;381(22):2135-44.

30. Lee EJ, Lee AI. Thrombocytopenia. Primary Care: Clinics in Office Practice. 2016 Dec 1;43(4):543-57.

31. Iolascon A, Andolfo I, Russo R. Congenital dyserythropoietic anemias. Blood. 2020 Sep 10;136(11):1274-83.

32. Steiner LA, Gallagher PG. Erythrocyte disorders in the perinatal period. InSeminars in Perinatology 2007 Aug 1 (Vol. 31, No. 4, pp. 254-261).

33. Mattina T, Perrotta CS, Grossfeld P. Jacobsen syndrome. Orphanet Journal of Rare Diseases. 2009 Dec;4(1):1-0.

34. Lansford R, Rugonyi S. Follow Me! a tale of avian heart development with comparisons to mammal heart development. Journal of Cardiovascular Development and Disease. 2020 Mar;7(1):8.

35. Ito N, Tsukamoto K, Taniguchi K, Takahashi K, Okamoto A, Aoki H, et al. Isolation and characterization of fetal nucleated red blood cells from maternal blood as a target for single cell sequencing-based non-invasive genetic testing. Reproductive Medicine and Biology. 2021; 20; 352-360.

36. Isern J, He Z, Fraser ST, Nowotschin S, Ferrer-Vaquera A, Moore R, et al. Single-lineage transcriptome analysis reveals key regulatory pathways in primitive erythroid progenitors in the mouse embryo. Blood, The Journal of the American Society of Hematology. 2011 May 5;117(18):4924-34.