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What Comes First, Chicken or the Egg? A New Perspective Based on the Diffusion Environment of Early Embryonic Life

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Introduction

A chick develops within an egg, yet encased in a rigid shell, it is insulated from the environment and lacks maternal support or any direct physiological nurture other than the warmth of the brooding hen. Still, the embryo grows, differentiates, and forms its own circulatory system [1,2]. This raises an intriguing question: how can a chick embryo survive and develop when it is apparently deprived of oxygen? [3]

The answer is simple. The eggshell appears solid but is actually not airtight. It is a hard, ceramic-like lattice of calcium carbonate perforated by approximately 7,000 to 17,000 microscopic pores [4-6]. Each act as a tiny channel through which gases such as oxygen and carbon dioxide move by passive diffusion, meaning they move from regions of high concentration to regions of low concentration without requiring energy [7]. Oxygen from outside moves in, while carbon dioxide produced by the embryo moves out [8]. This exchange follows the principles of Fick's law, in which the rate of diffusion is proportional to available surface area and inversely related to diffusion distance and barrier thickness [9,10]. Thus, the shell allows gases to pass through, while simultaneously providing mechanical protection and limiting water loss [11].

Beneath the shell, the extraembryonic membranes (specialized layers surrounding the embryo but not forming part of its body) develop and fuse to form the chorioallantoic membrane (CAM), a membrane involved in gas exchange and nutrient transfer [12,13]. This highly vascularized, capillary surface lies directly against the inner shell membranes, bringing embryonic blood close to the surface, thereby minimizing the diffusion distance and maximizing the surface area for gas exchange [14,15]. As the embryonic heart starts beating early in development, it distributes oxygenated blood throughout the organism. Thus, an internal circulatory system is established that operates independently of maternal supply [16].

As hatching nears, the embryo breaks into an air cell at the blunt end of the egg, which forms as the egg cools after laying [17]. This action shifts gas exchange from membranes to lungs [18]. Hours later, the shell cracks and the chick emerges, completing its transition to independent pulmonary respiration in the external world [19]. In mammals, a similar paradox exists. From ovulation to implantation, the human embryo survives for nearly a week without direct connection to maternal blood vessels [20,21]. During this period, it divides, activates its genome, and prepares for implantation, progressing through the cleavage, morula, and blastocyst stages as it travels from the fallopian tube to the uterine cavity [22-24]. This journey, typically lasting several days, occurs without any direct connection to the maternal circulation [25].

As in the egg, embryonic survival in mammals during this development depends on diffusion-driven mechanisms [26]. Oxygen and nutrients are derived from fluids in the surrounding reproductive tracts, which themselves are supplied by diffusion from maternal capillaries in the tubal and uterine tissues [27,28]. The embryo's small size, about 100 µm in diameter, keeps diffusion distances short, allowing passive exchange to meet its energy requirements [29]. During this phase, metabolic support is entirely histotrophic, which means it is derived from secretions of the tubal and endometrial epithelium rather than directly from maternal blood [30,31].

Discussion

The dilemma

Early embryonic life presents a striking physiological paradox: the apparent conflict between rapid cellular activity and non-vascular oxygen supply [32]. Rapid cell division, genomic activation, and early differentiation begin without a circulatory interface with maternal blood, depending entirely on oxygen delivered by passive diffusion [33,34]. Yet growth remains reliable and precise [35]. This leads to a fundamental question: why would such intense embryonic development occur in the absence of a vascular oxygen supply?

Why oxygen matters

The distribution of oxygen concentration across physiological compartments is highly variable [36]. Atmospheric air contains about 21% oxygen. As oxygen diffuses from the environment into the cellular interior, the oxygen concentration declines. For example, alveolar air typically measures approximately 13–14%, and arterial blood corresponds to approximately 12–13% expressed as an equivalent gas-phase fraction. As oxygen continues to diffuse into tissues, interstitial oxygen (oxygen found in the fluid between cells) normally ranges from 3–7%, and within cells, intracellular oxygen concentration is typically 2–5% [37-39]. Critically, in the tubal lumen and endometrial cavity, where early embryo development occurs, levels are between 2–8% [40,41].

Oxygen is critical because at the cellular level, it is the final electron acceptor in mitochondrial oxidative phosphorylation [42]. This is the process by which cells make energy in mitochondria. Electrons from metabolic substrates pass through the proteins of the electron transport chain at the inner mitochondrial membrane, generating a proton gradient that drives ATP synthesis [43]. Under aerobic conditions, approximately 30–32 ATP molecules are generated per glucose molecule [44]. By contrast, glycolysis in the cytoplasm produces only 2 ATP per glucose molecule, with most of the energy conserved in lactate and other reduced, energy-rich intermediates [45].

However, the energetic advantage of oxidative phosphorylation is not without cost. Inevitably, some electrons will escape from the respiratory chain and react with oxygen to form reactive oxygen species (ROS), such as superoxide and hydrogen peroxide [46]. These molecules can damage DNA, proteins, and cellular membranes [47]. Thus, oxygen, whilst essential, is also a potential source of molecular injury [48].

Embryonic vulnerability

Early embryos are particularly sensitive to oxidative stress [49]. During the pre-implantation period, cells undergo rapid DNA replication and gene regulation (epigenetic reprogramming) and begin to differentiate into distinct cell types (early lineage specification) [50,51], all of which demand exceptional stability of the cell's metabolic state. Even small increases in ROS exposure may have disproportionate and lasting developmental consequences [52].

The diffusion solution

Diffusion prevents abrupt oxygen surges [53]. Without maternal perfusion, highly oxygenated blood cannot suddenly flood the embryonic environment, and oxygen delivery remains gradual and buffered [54]. This reduces the risk of destabilizing redox balance during a developmentally sensitive period [55]. Diffusion also limits the rate at which oxygen and metabolic substrates can be delivered [56]. This creates a physical constraint that prevents mitochondrial activity from reaching high-flux states [57]. As a result, electron transport proceeds at controlled rates, avoiding excessive mitochondrial membrane potential generation and reducing electron leakage and ROS formation at their source [58-60]. This restrained energy configuration is called metabolic quietness [61]. Mitochondria remain functional, yet oxidative phosphorylation proceeds at moderate rather than maximal rates [62]. Oxygen delivery by slow, gradient-dependent diffusion establishes a protective, self-limiting system that regulates embryonic energy economy [63]. In this way, protection of genomic and epigenetic integrity arises from diffusion-mediated control of metabolic output and redox states [64]. Diffusion creates a buffered interface between the embryo and its surroundings that is not merely a transport system but a regulatory boundary, setting an upper limit on metabolic activity and thereby creating a regulated microenvironment that stabilizes risk exposure during periods of greater developmental vulnerability [65].

Substrate strategies

Early embryos preferentially utilize pyruvate and lactate, while glucose metabolism remains relatively limited [66,67]. This represents a strategic redistribution of ATP production towards glycolysis, yielding lower ATP output but reduced oxidative stress [68]. Pyruvate may also act as a direct scavenger of reactive oxygen species, converting hydrogen peroxide into less harmful products and thus contributing to antioxidant defence [69,70]. The outcome is not metabolic insufficiency but a deliberate energy strategy that prioritizes stability over maximal output, protecting the developing embryo during one of the most vulnerable periods of life [71,72].

Conclusion

Taken together, the avian and mammalian models reveal a shared developmental strategy that appears deeply conserved across vertebrate evolution. In both systems, early life unfolds in the absence of direct circulatory support and is sustained instead by diffusion-based gas exchange within a controlled microenvironment. Development therefore proceeds within

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a protected physiological window characterized by low mitochondrial activity and constrained metabolic flux, which limit oxidative stress and safeguard genomic and epigenetic integrity during this critical stage of life. This review proposes that, in evolutionary terms, a diffusion-regulated environment—a biological "shell," whether external, as in the avian egg, or internal, within the human reproductive tract—represents a necessary precursor to the subsequent establishment of perfusion. What may appear to be a limitation of early development is, in fact, a fundamental regulatory strategy that stabilizes redox balance at the very moment when developmental programs are most sensitive to disruption.

Recognition of this principle has important implications for reproductive medicine and obstetric pathology. Assisted reproductive technologies already reflect this understanding: embryo culture at reduced oxygen concentrations, typically around 5%, more closely approximates physiological tissue oxygenation and is associated with improved developmental outcomes compared with atmospheric conditions. Similarly, disturbances of the tubal or uterine environment — including infection, adenomyosis, or endometriosis — may alter this diffusion-regulated niche. Placental pathologies such as pre-eclampsia, foetal growth restriction, and early placental insufficiency may also reflect disruptions in oxygen regulation and mitochondrial function during the transition from diffusion-based support to perfusion. Viewed from this perspective, the longstanding question of whether the chicken or the egg came first appears resolved. The egg, a diffusion-governed developmental environment, represents the foundational milieu from which complex life, including that of chickens, emerges. Should we now dare to ask why the chicken crossed the road, the answer will surely lie in haemochorial transition, the reward of placentation reaching out to the other side.

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