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Termination of Organogenesis as Intrinsic Constraint on Animal Development and Evolution: A Theory

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Abstract

In this article, it is pointed out with integrative analysis that organogenesis manifests limitation in time and possession of termination, while infinite cell proliferation called as cancer and tumor is lethal. Besides, it is reversely demonstrated from a few notable constant outgrowing skin derivatives that termination is required for organogenesis inside the animal. Accordingly, it is suggested that the requirement for organogenetic termination would be the new intrinsic constraint for animal development and heredity. In further, it is suggested from comparative analysis that this new intrinsic constraint would not influence the temporal and spatial reorganization of morphogenesis, but place restrictions on alteration of organogenetic mechanisms themselves. Especially, it is pointed out that addition of new induction mechanism or elimination of termination mechanism would usually cause endless organogenesis and lethality, subjecting to restriction by the intrinsic constraint, while addition of new termination mechanism or elimination of induction mechanism not be affected by the intrinsic constraint, occurring more frequently in evolution. In accordance, it is identified this intrinsic constraint as the pertaining cause for frequent occurrence of developmental parallelism and terminal addition in animal evolution as recapitulation. In this article, it is also provided with some animal models to demonstrate the evolution of organogenetic termination as key developmental control, such as the hair and nail in humans, the sexual dimorphism in mammary glands, the epidermal scale in reptiles, the tail metamorphosis in amphibians, and the variation in limb digits in vertebrates.

Keywords

Organogenesis, Induction, Termination, Cancer, Intrinsic Constraint, Organ Regeneration, Evolution, Recapitulation

Subject Areas: **Developmental Biology, Evolutionary Studies, Genetics**

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1. Introduction

The study of development was dominated by the principle of recapitulation or biogenetic law in 1800s, as represented by Haeckel and von Baer. Nonetheless, as some exceptions have accumulated, the hypothesis of recapitulation is no longer universal [1]-[3]. In contrast, since Wilhelm Roux, embryologists have successfully revealed and demonstrated many developmental processes and mechanisms via experiments. Whereas, how developmental processes are correlated with evolution is still one of the most important subjects in life sciences, and has attracted the attention of many scientists recently [1] [3]-[5].

Most types of differentiated tissue cells were present early in animal evolution. Even the very primitive metazoan groups possess several cell types. The differentiated tissue cells of muscle, nerve, gut and epithelium among various animal species appear to be very ancient in origin and the majority of them to remain relatively stable during the long period of evolutionary process [1]-[5]. Whereas, the formation and organization of these different types of tissue cells into different organs of various shapes have changed dramatically in evolution and have thus generated the various species, such as the mammals, birds, and insects [1] [3]-[5]. In this regard, in this article the author will analyze deeply into the organogenetic processes and mechanisms in generation of morphological diversity of animals, attempting to reveal a new intrinsic constraint on development and heredity at the organizational level, and identify its effects on animal evolution, so as to interpret the phenomena related to recapitulation or biogenetic law of Haeckel and von Baer with the updated progressions of genetics and development at molecular and cellular level.

2. Requirement for Organogenetic Termination as Intrinsic Constraint on Development and Heredity

2.1. Four Cellular Processes for Morphogenesis of Organs and Tissues

Development is complex and comprises many different processes, including morphogenesis and differentiation. All organs are made of tissues, while organogenesis is actually the process of tissue formation and organization for the generation of an organ. Differentiation of tissues may also constitute a part of morphogenesis in some organs, such as the formation of bone and tooth, while differ in process from organogenesis in else, such as the synthesis of neuronal transmitters.

It is common knowledge that there are four types of tissues constituting the organs of animals, which are the nervous tissue, connective tissue, muscular tissue and epithelial tissue. The morphology of individual tissues is determined by the morphological constituents at cellular level, namely the cell number, position, shape and sometimes the secretes, manifesting also as four in cellular characteristics. For intuitive demonstration, the neuron number in cortex determines the cortical modality number in mammals, the neuron position in cortex arranges neurons into various laminates, and the neuron shape contributes to the formation of synapses and neuronal interactions [6]. In some other tissues and organs, such as the bone and tooth, cell secretes also constitute the morphological components of the organs.

In correspondence, morphogenesis of a tissue or organ also involves four cellular processes respectively as cell proliferation/elimination, migration, shaping and secretion. For intuitive demonstration, in the development of mammalian cortex [6], neuronal cells are generated at the germinal zones from precursor cells through cell proliferation. Later, the generated cells migrate to their corresponding cortical laminate. Finally, axons project out from the cortical neurons until they reach their targets. In some other tissues or organs, such as the bone and tooth, cell secretion also participates in the morphogenesis of the tissues or organs. In some special organs such as vertebrate limbs, programmed cell death finally modifies the shape of organ into appropriate for usage [7] [8]. Cell proliferation/programmed death, migration, shaping, and secretion make up the morphogenesis of tissues and organs.

2.2. Organogenetic Induction and Termination

Morphogenesis of an organ is initiated by inductive events. There are many types of inductive events. Some inductive processes occur very early in the gastrula stage and may be involved in the establishment of rudimental body plan. Organogenesis proceeds on the subsequent inductive events, initiating cell proliferation, migration, shaping and secretion for the generation of an organ. When reaching appropriate size and shape, morphogenesis of the organ terminates.

The cellular process of organogenesis manifests limitation in time and possession of termination, which is a common phenomenon widely present in all four types of tissues constituting the organs of animals. With regard to the nervous tissue, in the morphogenesis of cerebral cortex in monkeys, cortical neurogenesis starts around the 40th embryonic day, but stops at the 70th embryonic day in the limbic cortex and 100th embryonic day in primary visual cortex [6]. Adhesion to appropriate positions stops cell migration during cortical morphogenesis [6]. In the development of vertebrate nervous system, when the outgrowing axons reach their targets, the axons stop in growth and turn the neuron into final shape. Cell secretion does not play role in morphogenesis for nervous tissues. As to the connective tissue, in the morphogenesis of bone such as in growth, cell proliferation and secretion both terminate when reaching appropriate size and shape [9], whereas cell migration and shaping contribute little to the morphogenesis in connective tissues. In the morphogenesis of muscular tissues, miRNAs have recently been identified as participation in control of termination of cell proliferation [10], and cell elongation is terminated once reaching the terminal ends of their attached organs. Whilst, cell migration and secretion contribute little to the morphogenesis of muscular tissues. Finally, in the morphogenesis of epithelial tissues, contact inhibition is well known to terminate proliferation of epidermal cells [11], except in a few skin derivatives constant cell proliferation occurs on the surface of body without necessity for termination, such as the human nail adaptive to mechanical cutting, as manifested in many national and world records on length of it. Besides, migration of epidermal cells helps form invaginated hair follicles in vertebrates, while cell secretion forms chitinous cuticles in arthropods. Cell shaping plays little role in the morphogenesis of epithelial tissues. In all in accordance, limitation in time and possession of termination is widely present in morphogenesis of all four types of tissues constituting the organs of animals, except for a few constant outgrowing skin derivatives.

In addition, programmed cell death sometimes helps modify the final shape of some organs into appropriate for use, such as the digit separation in limbs [7] [8]. Likewise, together with osteoblasts and osteocytes, the osteoclasts help remodel the shape of various bones [12], most notably as the remodeling of oral bones. Hence, it is herein termed the termination directly against organogenesis as primary termination or simply as termination, while the additional processes modifying the final shape of some organs as accessory termination. The rationality of this classification is supported by the tail degeneration during amphibian metamorphosis, in which programmed cell death removes the whole organ of the tail [13] [14].

2.3. Termination as Organogenetic Constraint

More importantly, if viewed at the organizational level in animals, termination of morphogenesis of organs in further plays a key role in controlling organogenesis more than induction. Without termination, morphogenesis of an organ would proceed infinitely, disorganizing the overall morphology and causing lethality, especially with excessive cell proliferation and secretion. Infinite cell proliferation due to loss of contact inhibition is called as cancer [11], and is lethal. Cancers and tumors occur in most organs, demonstrating the potency of the organs to transform into infinite cell proliferation. On the other hand, constant skeleton growth would not favor a vertebrate to move and is lethal either, just as the whale can only live in ocean but would die on land from skeleton overloading. In collection, requirement for organogenetic termination is an intrinsic constraint on animal development and heredity at the organizational level.

A few notable exceptions to this intrinsic constraint deserves special attention, in which constant cell proliferation or secretion occurs on the surface of body, mostly as skin derivatives, so that no longer disrupts the internal organization and overall morphology of animal. The epidermal scales in reptilian species are continually thickened due to continual proliferation of epidermal cells, with the outer layer of the epidermal scales shed in lizards and snakes [15] [16], and worn off by abrasion in some crocodilians [17]. Likewise, the human nail can grow all lifelong due to cell proliferation without termination, as manifested in many national and world records on length of it. In reverse, these few skin derivatives notably of constant cell proliferation or secretion on the surface of body also demonstrate in turn that cell proliferation or secretion inside the body of animal must be terminated for development and heredity to avoid disrupting the internal organization and overall morphology.

In collection herein, termination is special in that it is intrinsically required for animal development and heredity to prevent endless organogenesis and congenital dysmorphosis, which is supported in three aspects: 1) Organogenesis manifests limitation in time and possession of termination, which is widely present in all four types of tissues in animals, except in a few constant outgrowing skin derivatives. 2) Infinite cell proliferation called as cancer and tumor is lethal, while whales with skeleton growth more than terrestrial animals can only live in ocean but would die on land from skeleton overloading. 3) The few notable skin derivatives of constant

cell proliferation or secretion on the surface of body reversely demonstrate that cell proliferation or secretion within the body of animal must in turn be terminated for development and heredity to avoid endless organogenesis and congenital dysmorphosis.

3. Two Forms of Genetic Changes in Animal Morphogenesis

Genetic changes of animal morphogenesis can be classified into two categories. One category of morphogenetic changes may only involve the temporal or spatial reorganization of the existing morphogenetic processes, while another category of morphogenetic changes directly involve the alteration in nature of organogenetic mechanisms themselves.

Genetic changes involving only the temporal and spatial reorganization of existing morphogenetic processes occurred often in animal evolution. There have been efforts to create some temporal models to demonstrate the heterochrony with changes in time of developmental events in animals [1] [3], with many examples fitting into the models. Spatial alteration of animal morphogenesis can be best represented as example by the generation of different spiral patterns in Lymnaea peregra. In this case, the generated dextral and sinistral forms in adult Lymnaea peregra is determined by the earliest spiral cleavage patterns [18]. As the two forms of Lymnaea peregra are interchangeable through hybridization, there should have been some genetic changes as spatial rearrangement of morphogenesis that occurred in evolution to generate the different morphological forms in this species.

Genetic alteration in the nature of organogenetic mechanisms themselves may also cause changes in morphology of animal, which is more easily demonstrated with genetic and comparative studies at molecular and cellular level. To further distinguish this concept from the temporal and spatial reorganization of existing morphogenetic processes, it is herein to inspect the development of mammary glands. On the one hand, there are different numbers of mammary glands in various mammals which may even be located at different positions on the abdominal surface of body. Changes in location of mammary glands in evolution just represent spatial translocation of mammogenesis. On the other hand, during mammary development, the vigorous proliferation of ducts and alveoli in pregnancy and lactation may be induced by several hormones, notably by growth hormone, prolactin, placental lactogen and so on [19] [20]. Whereas, the primitive mammary glands are present in monotremes which are not viviparous [21], so that the precursor mammary glands should not have possessed this pregnancy-related mammogenesis. Therefore, this hormonal-controlled cellular proliferation in mammary glands in pregnancy is a new morphogenetic mechanism acquired recently in evolution. This case represents a genetic change in the nature of organogenetic mechanism itself via introduction of a new inductive event for cell proliferation.

Genetic changes involving the nature of organogenetic mechanisms themselves may in further be classified into several forms in animals. Changes in mechanisms of organogenesis may introduce a new organogenetic mechanism, eliminate some existing mechanisms, and may also change an existing mechanism into another novel mechanism. In fact, the latter form of change in mechanism can be understood as simultaneously introducing a new mechanism while disrupting an existing mechanism. In this regard, all changes in mechanisms of organogenesis in animals can ultimately be classified into the two forms as introduction of a new organogenetic mechanism and elimination of some existing organogenetic mechanisms. The above mentioned evolutionary acquisition of pregnancy-controlled cellular proliferation in mammary glands was the introduction of a new inductive event, whereas the constant growth of human hair instead resulted from the evolutionary elimination of termination in growth of original short hair in apes as neutral genetic mutation adaptive to mechanical cutting, as manifested in many national and world records on length of human hair.

In brief, genetic changes of animal morphogenesis can be classified into two categories. One may only involve the temporal and spatial reorganization of existing morphogenetic processes, while another involves the changes in nature of organogenetic mechanisms themselves.

4. Organogenetic Termination as Intrinsic Constraint on Development and Heredity in Evolution

4.1. The Effects of the Intrinsic Constraint on Temporal/Spatial Reorganization of Morphogenesis

As the genetic changes of morphogenesis can be classified into two categories either as the temporal/spatial re-

organization of existing morphogenetic processes or as the changes in nature of organogenetic mechanisms themselves, it is interesting to inspect the different effects of this intrinsic constraint on the two categories of morphogenetic changes during animal evolution.

With regard to the genetic changes as temporal and spatial reorganization of existing morphogenetic processes in animals, organogenesis in descendents would certainly be terminated in the same way as in progenitors. No matter in the cases fitting in the temporal models created by some scientists recently [1] [3], or in the two dextral and sinistral forms of Lymnaea peregra representing spatial rearrangement of morphogenesis [18], termination mechanisms of morphogenesis all preserved in the same way as in progenitors. In this regard, the intrinsic constraint requiring organogenetic termination would not affect the temporal and spatial reorganization of morphogenetic processes in animals.

4.2. The Effects of the Intrinsic Constraint on Addition of Organogenetic Mechanisms

The intrinsic constraint requiring organogenetic termination would place some new restrictions on alteration of organogenetic mechanisms themselves in animal evolution, which is easily demonstrated with genetic and comparative studies at molecular and cellular level. Addition or alteration of an induction mechanism for organogenesis would have to be confronted with the requirement of termination against the organogenesis initiated by the newly introduced induction in animals. Without termination, the newly acquired organogenetic process would also proceed infinitely and cause lethality. In this regard, requiring termination would exert an additional constraint on genetic addition or alteration of induction mechanisms for organogenesis. However, in a few special cases, a new induction mechanism may have been introduced in animal evolution as it just happened to be able to make use of some existing mechanisms for termination. For instance, as stated above, the cellular proliferation in mammary duct and alveolus was the consequence of genetic addition of novel organogenetic induction by pregnancy and lactation [21], especially induced by several hormones such as growth hormone, prolactin, placental lactogen and so on [19] [20]. Nonetheless, these hormones decline with the termination of pregnancy and lactation so as the evolutionary addition of this hormonal induction of mammogenesis happened to make use of the existing decline in hormonal secretion as termination.

Some inductive events for other purposes may occur at earlier developmental stages than the induction of organogenesis, such as the determination of cell fates at the earliest embryonic stages, the establishment of rudimental body plan and so on. Changes in these early induction mechanisms rather than organogenetic induction are irrelevant to the intrinsic requirement of organogenetic termination to stop the organogenesis initiated by organogenetic induction, so that would not be restricted by this intrinsic constraint on animal development and heredity. For instance, the direct-developing sea urchin without larval stage may have evolved from indirect-developing sea urchins with larval stage through extensive remodeling in early stage in localization of maternal determinants in oocyte and dissociation of cell cleavage from axis formation [2], while preserved in making use of all the later organogenetic mechanisms.

It is important to point out that addition of an induction mechanism of organogenesis via duplication of an existing induction mechanism should certainly be able to make use of the termination mechanisms of original organogenesis, and would have occurred more frequently in animal evolution without affected by the intrinsic constraint requiring organogenetic termination, which is a part of developmental parallelism in evolution some authors adopted to account for organogenetic recapitulation [1] [22].

Addition of new termination mechanisms to the existing organogenetic processes in animals would make the descendents possess more termination mechanisms for stopping organogenesis than their progenitors, so that not be affected by the intrinsic constraint requiring organogenetic termination. In higher mammals, although the mammary rudiments develop in both sexes in their embryos, the morphogenesis of mammary glands in male embryo is terminated early in response to testosterone before the formation of any ductal structures, while it still continues in female embryo due to the lack of testosterone [23]-[25]. Since the primitive mammary glands are present in both sexes in monotremes [21], it is likely that it is the testosterone-related male termination mechanism of mammogenesis that was added more lately in evolution to the original mammogenesis. This is an example as terminal addition of developmental mechanism in animal evolution.

Addition of accessory termination mechanisms should not be constrained by the intrinsic requirement for organogenetic termination either, as the descendents would likewise possess more termination mechanisms to stop

organogenesis than their progenitors. Some functional larval structures of amphibians such as the tail of tadpole are absorbed as a whole during metamorphosis with programmed cell death [13] [14], representing the addition of accessory termination mechanisms for degeneration in animals. Likewise, in higher vertebrates, local programmed cell death in limb interdigital zones is a degenerative process accessory to the termination mechanisms against organogenetic proliferation, necessary for the separation of digits [7] [8]. However, the development of free digits in amphibians does not involve cell death [26]. Obviously, the local programmed cell death in interdigital zones was lately acquired in higher vertebrates in evolution as accessory termination for partial modification of final morphology to separate digits.

As the intrinsic constraint requiring organogenetic termination has not placed any restrictions on evolutionary addition of new termination mechanisms and accessory termination mechanisms, addition of these mechanisms would certainly have occurred frequently in animal evolution. This is exactly the pertaining cause of terminal addition of developmental processes in animal evolution some authors termed [27] [28], a part of recapitulation too.

It is necessary to point out that exposure to environmental adaptation or natural selection is not the reason for causing terminal addition. As having been demonstrated, duplication of the earlier organogenetic induction also occurs freely and is terminated as in original, which is obviously also subject to environmental adaptation or natural selection.

Herein, it is accounted for the developmental parallelism and terminal addition as two branches of recapitulation with the intrinsic constraint requiring organogenetic termination. Recently, it was demonstrated with computational system that recapitulation indeed occurred as higher in frequency during animal evolution [29]. In this regard, this intrinsic constraint is certainly in turn identified as the pertaining cause for the aptly frequent occurrence of recapitulation.

4.3. The Effects of the Intrinsic Constraint on Elimination of Organogenetic Mechanisms

In contrast, elimination of organogenetic mechanisms has been less studied in comparison to addition. Elimination or disruption of organogenetic induction would lead to deletion of the whole subsequent organogenetic processes initiated by the inductive event in animals, so that it would not cause endless organogenesis, nor be restricted by the intrinsic constraint requiring organogenetic termination. It has been shown that the evolutionary loss of teeth in birds was the result of dysfunction in induction mechanism for tooth morphogenesis [30], while in similar the specific absence of external granule layer of cerebellum in non-teleost ray-finned fish was likely due to the genetic loss of gene expression of *Sonic hedgehog* driving cell proliferation there [31].

Nonetheless, as the organogenetic termination functions to stop organogenesis, elimination of termination mechanisms would have to run the risk of causing endless organogenesis. In this regard, the intrinsic constraint requiring organogenetic termination would place restrictions on elimination of organogenetic termination, making the animal die and disappear. Nonetheless, when the resulted constant organogenetic growth happened on the body surface protruding outward without causing morphological disorganization, elimination of termination may be observed in animal evolution. It is common knowledge that the human skull hair can grow continuously in length if not cut mechanically, as manifested in many national and world records on length of it. It was evolved from the short hair in apes, and was obviously acquired in human evolution as elimination of termination for hair growth via mutations neutral to mechanical cutting. Similar story occurred to the evolutionary acquisition of constant growth of human nail with many national and world records on length of it too.

Elimination or disruption of accessory termination mechanisms may not necessarily eliminate (primary) termination against organogenesis, nor cause endless organogenesis, so that nor necessarily be restricted by the intrinsic constraint requiring organogenetic termination. In vertebrate limb development, interdigital cell death is the accessory termination mechanisms helping to separate digits. Partial dysfunction of this process in web-footed birds, as characterized by smaller scale and shorter duration, has not led to endless limb growth but just annealed the toe digits [7].

4.4. Summary of the Effects in Evolution

In brief, the various genetic changes in organogenetic induction and termination during evolution are summarized in the following table with regard to the constraint requiring organogenetic termination.

	Temporal/spatial change	Addition	Elimination
Organogenetic induction	No constraint	Constraint	No constraint
Organogegetic termination	No constraint	No constraint	Constraint

5. Brief Perspectives

The new constraint requiring termination for organogenesis would significantly deepen the hereditary understanding of animal development and evolution. It is a new hereditary constraint for animal development, which potentially benefits to the therapeutic research of cancers and tumors, the biomedical research on organ regeneration from stem cells, the biological research in developmental control and adaptive skin derivatives, and so on. It is also a new hereditary constraint for animal evolution, which not only accounts for the recapitulation as the frequent occurrence of developmental parallelism and terminal addition in animal evolution, but also potentially becomes a more general rule than recapitulation in providing explanations to the organogenetic exceptions of recapitulation as degenerative elimination of inductive or accessory termination mechanisms.

Due to the importance of organogenetic termination, it is necessary to choose some valuable animal models for further genetic and comparative studies at molecular and cellular level in future. The hair and nail in humans versus in primates, the sexual dimorphism of mammary glands in mammals, the epidermal scale in reptiles, the metamorphosis of tail in amphibians, as well as the variation in limb digits in vertebrates are all good models for demonstration of genetic variations in organogenetic termination in animals.

6. Conclusions

In this article, it is pointed out that the cellular processes of organogenesis manifest limitation in time and possession of termination, which is widely present in all four types of tissues constituting the organs of animals. Without organogenetic termination, organogenesis would usually proceed on infinitely and result in lethality. Infinite cell proliferation from mutations is called as cancer and tumor, and is lethal. Cancers and tumors occur in most organs, demonstrating the proliferative potency of the organs. Besides, the few notable cases of constant cell proliferation or secretion on the surface of body as skin derivatives also reversely demonstrate that cell proliferation or secretion within the body of animal must in turn be terminated for development and heredity to avoid endless organogenesis and congenital dysmorphosis. In accordance, requirement for organogenetic termination is a new intrinsic constraint on animal development and heredity.

This intrinsic constraint requiring organogenetic termination would not affect the genetic changes only involving the temporal and spatial reorganization of morphogenesis in animal evolution. Nonetheless, the new intrinsic constraint would place some restrictions on alteration of organogenetic mechanisms themselves in evolution. Addition of new induction mechanism or elimination of termination mechanism in animals would usually cause endless organogenesis and be lethal, so that be restricted by this intrinsic constraint, except the newly added inductive mechanisms happened to be able to make use of the existing mechanisms for termination or the endless organogenesis with termination mechanism eliminated happened to situate on the surface of body without disturbing the overall organization of morphology. It is necessary to point out that change in inductive events for purposes other than organogenesis at earlier developmental stages is irrelevant to the intrinsic requirement of organogenetic termination to stop the latter organogenesis initiated by organogenetic induction, so that would not be restricted by the intrinsic constraint.

In contrast, duplication of existing induction mechanism would certainly be able to make use of the existing termination mechanisms against organogenesis, nor be restricted by this intrinsic constraint, so that occurred more frequently in evolution. Likewise, addition of new termination mechanism would not be restricted by this intrinsic constraint either, nor would the change in accessory termination mechanisms necessarily be restricted by the intrinsic constraint, so that also occurred more frequently in evolution. In this regard, this intrinsic constraint requiring organogenetic termination is identified as the pertaining cause for the frequent occurrence of developmental parallelism and terminal addition in animal evolution as recapitulation. Besides, the intrinsic constraint requiring organogenetic termination in further enriches our knowledge on genetic elimination of organogenetic mechanism as either induction or termination during animal evolution.

In this article, it is provided with some valuable animal models to demonstrate the evolution of organogenetic

termination as key developmental control, such as the hair and nail in humans versus in primates, the sexual dimorphism of mammary glands in mammals, the epidermal scale in reptiles, the metamorphosis of tail in amphibians, and the variation in limb digits in vertebrates, making it convenient for genetic and comparative studies at the molecular and cellular level.

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