Emerging Models of Angiogenesis Patterns and Response Effect of Endothelial Cells

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Abstract: Through the comparison and analysis of the angiogenesis conditions for different pathophysiologic states, such as growing process of the animal, tumor growth, and wound repair, an index of the hypoxia intensity is proposed to evaluate the environment of angiogenesis, based on which the mechanism of the angiogenesis patterns under different environment is discussed. A new concept of response effect is deduced for describing the reaction of the endothelial cell (EC)s towards the VEGF concentration in the microenvironment during the angiogenesis, and an explanation for different angiogenesis patterns of capillaries is given. At the same time the biological proofs cited from recent studies are provided to prove the response effect of the EC. With the results we try to show that in the pathophysiologic environment with high hypoxia intensity, the angiogenesis comes into being mainly by sprouting; while the hypoxia intensity is low, the angiogenesis mainly occurs through the intussusception. This concept shall offer a new basis and idea for the study of the capillary network construction, related clinical therapy, and induction of vascularization in the biomaterials.

Keywords: Angiogenesis, sprouting, intussusceptions, hypoxia intensity, VEGF.

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1. Introduction

In order to explore the process of vascularizing in biomaterial, we investigated the modes of angiogenesis patterns and the microenvironment in which they are formed. This paper is a progressing report of working in the studies, which include the reviews of correlative studies.

Angiogenesis [1] is a physiological process in which new blood vessels grow from pre-existing vessels by sprouting or through the intussusception. This process is a cascade process which involves accurate regulation of multiple factors [2]. It is known that the basic reason for angiogenesis is ischemia or hypoxia, which causes the regulation of many vascular growth factors, and VEGF is the main vascular growth factor among these factors. The cell culture in vitro shows that hypoxia induces the boosting up of the VEGF transcription [3]. In vivo experiment also shows that ischemia or hypoxia causes the increasing expression of VEGF [4], and at the same time the expression of VEGF receptor will also increase [5]. Sprouting and intussusception are the two main patterns of the angiogenesis, which are observed largely for confirming the patterns. Various factors affecting the angiogenesis patterns are investigated. Such factors include velocity of blood flow, shear stress of the flow to the vessel, etc. However, researches on emerging mechanism of the angiogenesis patterns are still rare; the problem that the different angiogenesis patterns happen under what kind of conditions is still not elucidated.

In order to resolve the problem, in this study, the index of the hypoxia intensity is proposed to assess the angiogenesis environment. Through comparison and analysis of the angiogenesis conditions in different pathophysiologic states, such as the growing process of the animal, tumor growth and wound repair, emerging mechanism of the angiogenesis patterns are discussed. The response effect of ECs towards the VEGF concentration is defined for describing the actions of ECs in different microenvironment during angiogenesis process. Based on the theory of response effect of ECs, we tried to explain the mechanism of different angiogenesis patterns. At the same time the biology proofs cited from the present researches was showed to prove the response effect of ECs. The results are useful to show that in the pathophysiologic environment with high hypoxia intensity, the angiogenesis comes into being mainly by sprouting; while when the hypoxia intensity is low, the angiogenesis occurs mainly through the intussusception, which is an important basis for the emerging pattern of angiogenesis. This theory will afford a new basis and idea for the study of the capillary network construction, related clinical therapy, and induction of vascularization in the biomaterials.

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2. Hypoxia intensity during the angiogenesis

In order to analysis the angiogenesis characteristic under different conditions, such as the growing period, the tumor, and the wound repair, taking note of the especial effect of the hypoxia, the difference of the hypoxia state in tissue should be firstly expressed by some index. It is noticed that hypoxia will cause the angiogenesis process, in which the capillary growing speed may reflect the hypoxia intensity indirectly. Therefore, we pay attention to the capillary growing speed in angiogenesis when the tissue is under different conditions. Thus the volume $V(t)$ of the local tissue in time t should be regarded as the analysis object. In the tissue the number of the capillaries is expressed by the total number of the capillaries with a certain length (for instance, the approximate average length is about 750 μm), and is written as $N(t)$. In all kinds of physiology and pathology process, when the cells proliferate or the metabolic process speeds up in the tissue, the original capillaries cannot satisfy the requirements of supplying blood and oxygen, and the tissue will be in hypoxia state, which will cause a series of angiogenesis processes and the supporting processes starting from the enhancement of the VEGF transcription, for reinforcing the deficiency of blood and oxygen supply. At this time the results of angiogenesis are the increase of the capillary quantity and adjustment of the density, and the results differ greatly when the hypoxia state differs. Let the increased capillary quantity in $V(t)$ time interval $(t, t+\Delta t\ ]$ be $\Delta N(t)$, therefore, in unit time and unit volume, the increased capillary quantity $\theta_T(t)$ is

$$\theta_T(t) = \frac{1}{V(t)} \frac{\Delta N(t)}{\Delta t}. \qquad (1)$$

The equation expresses the increasing intensity of the capillary quantity at time t. If the increase of the capillaries is considered as the effect of tissue ischemia and hypoxia caused by cell proliferation or metabolism reinforcement, $\theta_T(t)$ will express extent of the oxygen requirement in tissue, and can be used as the index to evaluate the angiogenesis environment indirectly, and is named as hypoxia intensity. In the study the hypoxia intensity is regarded as the index to assess the characteristic of angiogenesis; and its unit will be $1/mm^3d$ if the time unit is 1 day. In the following sections, assessment and comparison on various angiogenesis environments will be done during several typical physiology and pathology processes.

(1) Hypoxia Intensity during the growth period

During the growth period of human or animal, the angiogenesis must keep on due to the need of growth and metabolism reinforcement. Assume that during the above-mentioned growth process of the local tissue the metabolic rate in tissue remains stable. Let the capillary density be $\rho = N(t)/V(t)$. The capillary density will decline with the increase of the body volume, which will cause the tissue hypoxia and the angiogenesis, and finally make the capillary density recover to the original level. In such persistent dynamic process of tissue growth and angiogenesis, the capillary density ρ will always remain averagely invariable, thus the stable need of metabolism is satisfied.

Let the volume $V(t)$ increase to $\Delta V(t)$ during the growth period $(t, t+\Delta t\ ]$. To maintain stability of the capillary density, the capillary quantity will increase $\Delta N(t) = \rho \Delta V(t)$. Thus the hypoxia intensity at this time may be expressed as

$$\theta_T(t) = \frac{\rho}{V(t)} \frac{\Delta V(t)}{\Delta t}. \qquad (2)$$

During the animal growing period, when the capillary density is approximately invariable, the hypoxia intensity can be inferred as long as the volume growing rate $\Delta V/\Delta t$ is estimated. For instance, during the human growth period, the weight of the human skeleton muscle increases from 14kg to 15.2kg for about one year. Assume that the specific gravity of the muscle is about 1.2kg/ m^3d, and that the capillary density ρ is about 300 per mm^3, it can be computed that in one year the average capillary quantity is required to add 34.3 in one mm^3, that is, the hypoxia intensity during the human growth period should be that $\theta_T(t) \approx 0.095$ per mm^3d. Actually, during the growth period, the metabolic rate in the organism may vary in different phases. For example, in embryonic phase the metabolism is very strong, and the organism grows quickly, and thus its hypoxia intensity has great difference with that of the adult. On the other hand, when the animal stops growing, the hypoxia intensity $\theta_T(\infty) \to 0$, which shows that the capillary quantity stops increase and is in a dynamic equilibrium state.