Controlling collateral development: the difficult task of mimicking mother nature

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In small animals with a relatively simple structure and organization, direct diffusion is sufficient for the transport of nutrients, gases and waste materials to and from individual cells. However, in the evolution of the higher metazoan animals, some cells become distant from the external environment, creating evolutionary pressure for selection of those with rudimentary circulatory systems [1]. Thus, large multicellular organisms developed complex, cell-lined, vascular systems, allowing transport of water, ions and nutrients to remote parts of the organism, and removal of waste products.

Complex organisms developed reliable means to control the development of the circulatory system during embryogenesis (vasculogenesis), as well as mechanisms to compensate for the loss of segments of the circulatory system. This compensation can be achieved through the formation of new collateral vessels without a media layer (angiogenesis), and through the enlargement of smaller, pre-existing, vessels into full arteries possessing a media layer (arteriogenesis). However, these natural processes of collateral development appear to be primarily mechanisms for survival, and are often inadequate for full recovery of normal vascular function. Because of this limitation, they are able to deliver normal perfusion to tissues at rest, but are unable to cope with increased metabolic demands of stress or exercise.

Currently, it is unknown when the first angiogenic molecule appeared during evolution, but some authors speculate that certain growth factors, such as fibroblast growth factors (FGFs), are contemporary with triploblast phyla and may not exist in diploblast species [2]. These growth factors are highly conserved, with more than 92% sequence identity within the core region [3], underscoring their importance throughout mammalian evolution.

Normal human hearts characteristically contain small collateral vessels, whereas hearts from patients with angina [4] and following acute myocardial infarction [5,6] typically possess much larger collateral vessels. Such collateral vessels can develop both at the epicardial and subendocardial levels [7,8]. The extent of collateral development is related both to the duration [9,10] and severity of coronary arterial narrowing [10,11]. Collateral expansion can improve myocardial perfusion in areas of ischemia, preserving myocardial viability and function even when a large epicardial coronary vessel is totally occluded [12]. In patients with an acute myocardial infarction, the adequacy of pre-existing collateral vessels influences infarct size, the volume of viable myocardium, the formation of left ventricular aneurysms, and prognosis [13–16].

If we were able to understand the complex molecular and cellular mechanisms involved in the natural process of collateral growth, we might be able to potentiate this process. Such an approach could lead to important therapeutic strategies for the management of two of the major causes of death and disability in Western countries, namely, coronary and peripheral artery disease.

Long after the pioneering work of Beck at the Cleveland Clinic, who attempted to induce the growth of coronary collaterals through the application of asbestos powder into the pericardial cavity, a number of angiogenic growth factors were characterized and purified, including FGF-1, FGF-2, VEGF, IGF, scatter factor, and many others. The complete molecular structures of many of these growth factors have been identified, and their genes have been cloned and expressed through recombinant technologies.
We have learned from experimental animal models that significant improvements in collateral development, both in the heart and in the peripheral circulation, can be achieved through administration of angiogenic growth factors. However, it is premature to gauge if the exciting results obtained in animals can be recapitulated in humans. Preliminary reports from Phase I and II clinical trials have shown that the administration of these growth factors is feasible. However, results have been conflicting with respect to the demonstration of a salutary biologic effect. Whereas reports from uncontrolled Phase I studies and some Phase II trials have been encouraging [17–22], results of a larger, controlled Phase II study have been negative [23]. Major concerns associated with angiogenic growth factor administration include their potential long-term impact on tumor growth, atherosclerosis and restenosis. Given the negative results of the Phase II study, and in light of these concerns, the early enthusiasm seen in this field has been replaced by a more cautious attitude. The results of ongoing clinical trials are eagerly awaited; however, it is clear that much basic science remains to be learned before a rational, directed approach to angiogenic therapies is feasible.

In conclusion, during the last 30 years, we have been trying to understand the secrets behind one of the most important survival skills developed by mother nature, i.e., the development of collateral vessels. The evolution of knowledge has been great. However, it is probably naive on our part to think that mankind can unravel, in just a few decades of work in small laboratories, the mysteries of all of the layers of adaptation that required several million years to build in the largest laboratory, earth. Nonetheless, given our intense commitment to achieve this goal, it is our belief that the question is not if we will attain it, but when, how and at what cost.

References