An Inconvenient Truth: Recognizing Individual Differences in Arteriogenesis

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The Uniqueness of the Individual

In his essay entitled "*The Uniqueness of the Individual*" published in 1957, the Nobel Prize laureate Peter Medawar described how the tremendous genetic diversity of individuals within a species enables the species as a whole to survive[1]. At same time, his essay highlights that individual genetic diversity also poses a major challenge for the medical profession when trying to treat individuals. Although Medawar focused on genetic immunological diversity in the context of immunological tolerance to enable therapeutic transplantation of tissues and organs, the basic concept of diversity being a major benefit as well as a challenge is applicable to all aspects of human existence, from artistic creativity to social structures. In medicine, the recognition of the importance of individual diversity is common-place and has been incorporated into the day-to-day practice in the field of transplantation medicine and immunology. More recently, it is gaining recognition and acceptance in other fields of medicine, too, and has given rise to the concepts of pharmacogenomics and individualized medicine, in which medical therapies would be tailored to specific gene expression and drug response profile of the individual patient [2].

Genetic profiling of patients is rarely performed in the practice of cardiovascular medicine but data is emerging that, for example, patients may differ in their responses to drugs such as aspirin, though there is significant controversy in this area[3]. Even in emerging cardiovascular therapeutic approaches, such as those directed at enhancing blood vessel growth, there is a lack of standard patient profiling and individualizing therapies. One major reason is that many underlying mechanisms of blood vessel growth and inter-individual differences in blood vessel growth are still not fully understood[4, 5].

The study by Schirmer et al published in this issue of *Circulation Research*[6] takes an important step into this direction by using a microarray-based approach and studying patients with different propensities to grow compensatory collateral arteries in patients with coronary artery disease.

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Therapeutic Arteriogenesis and Individual Differences

The term angiogenesis is frequently used to describe all forms of blood vessel growth, both detrimental blood vessel growth as it occurs in cancer or diabetic retinopathy as well as beneficial compensatory blood vessel growth in cardiovascular ischemia. Since the growth of compensatory collaterals involves the growth of mature arteries, it is referred to as arteriogenesis. Ischemic tissue attempts to initiate the growth of blood vessels or recruitment of pre-existing blood vessels, however, significant differences exist between patients in their ability to grow or recruit compensatory blood vessels[4, 5]. Therefore, therapies are being developed to help restore blood vessel supply to the ischemic tissue using therapeutic angiogenesis/arteriogenesis with genes, proteins or cells.

Interestingly, even though results from animal studies and early clinical studies using angiogenic / arteriogenic proteins or genes have been very encouraging, larger randomized trials have not yet conclusively demonstrated clinical benefits[7]. As an alternative approach to augmenting blood vessel growth, cell therapies using either bone marrow derived mononuclear cells or progenitor cells / stem cells have been developed and so far early clinical studies and animal studies have also been positive[7]. However, larger randomized placebo-controlled trials are still lacking, and a recent meta-analysis of the smaller clinical trials with bone-marrow derived cells pointed out that the overall clinical improvements may be more modest than previously assumed[8].

Many reasons for the apparent discrepancy between animal studies or early small clinical studies of angiogenic/arteriogenic factors and the larger studies have been proposed[7]. One of the most compelling potential explanations is that patients differ significantly in their responses to angiogenic or arteriogenic factors and that animal studies or small clinical studies are likely to have a homogeneous group of therapy recipients. On the other hand, larger clinical trials have a broad heterogeneity of patients with different cardiovascular risk factors and life-style, medication compliance, pathophysiology and endogenous expression of growth factors or cytokines.

The paper by Schirmer at al studies patients with heterogeneous collateral growth response to coronary disease, in an attempt to understand the underlying mechanisms. Using microarray analysis of monocytes in coronary artery disease patients with higher (responders) and lower (non-responders) degree of collateral formation, the authors show that even though there is no significant difference in the gene expression of monocytes at baseline, multiple genes are expressed differentially after stimulation with LPS (lipopolysaccharide). Amongst the more prominent changes, the authors note that interferon-β and related genes in the interferon- β signaling pathway are over-expressed in LPS stimulated monocytes of non-responders.

Arteriogenesis and Interferon-β

Isaacs and Lindenmann[9] coined the term "interferon" to describe a novel secreted factor that could "interfere" with viral activity in the 1950's. It was not until the 1970's and 1980's that the interferons were identified, sequenced and recognized as a family of cytokines[10]. Currently, interferon-α and interferon-β as well as multiple newer members of the interferon family are considered to belong to be Type I interferons, while interferon-γ is considered a Type II interferon[11]. Multiple signaling pathways are activated by interferons, but one of their major roles is that they act as a defense mechanism against viruses and bacteria[10]. This may explain from a teleological point of view why interferon expression is activated by viral DNA/RNA and microbial products such as LPS via Toll-like receptors. In addition to their pro-inflammatory and host defense functions, interferons also have anti-inflammatory effects, which is why interferon-β is used as a therapy for autoimmune diseases such as multiple sclerosis[12].

Although the *anti-angiogenic* effect of interferon-β has already been known for over 20 years[13], the study by Schirmer et al is the first to demonstrate that it is also *anti-arteriogenic*. Based on this supporting evidence from a mouse model, the increased interferon-β expression found in LPS-stimulated monocytes of coronary artery disease patients may relate to their inability to develop sufficient collaterals. However, a major assumption is that the LPS-induced difference in monocyte gene expression relates to the development of collateral blood vessels. While it has been shown that microbial product LPS is a potent inducer of blood vessel growth via monocyte recruitment[14], its relevance for coronary artery disease is not clear.

Furthermore, interferons are induced by LPS and other activators of toll-like receptors. Therefore the differences between the monocytes of the two patient groups found by Schirmer et al may just point towards differential monocyte responses to LPS, but not necessarily to a central role for interferon-β in collateral development. Further studies are required to test if monocyte gene expression between the patient groups differs when using other physiological or pathophysiological stimuli found in patients with coronary artery disease, such as hypoxia or inflammatory factors.

Challenges that lay ahead for individualized therapies targeting arteriogenesis and angiogenesis

The paper by Schirmer et al makes the important point that over-expression of anti-arteriogenic factors may partially explain why patients may differ in their endogenous ability to develop collateral blood vessels and in their response to an arteriogenesis-enhancing therapy. Therapeutic agents, for example, may not be able initiate adequate blood vessel growth, if endogenous anti-arteriogenic factors within the ischemic tissue are interfering with blood vessel growth. However, it is equally important to realize that cytokines such as interferon-β are major regulators of the immune response and even used as therapies to treat autoimmune disease[12]. Therapeutic inhibition of interferons to promote blood vessel growth could have the side effect of activating autoimmune processes.

The close link between angiogenesis/arteriogenesis and inflammation is one of the major future challenges for the development of individualized therapies directed at enhancing blood vessel growth, since it requires the development of approaches which selectively favor signaling pathways that minimize inflammatory side-effects[15]. Another important key task is to identify methods that allow for the assessment of individual patient needs by evaluating the transcriptome, proteome and functionome of endogenous cells involved in blood vessel growth, both at baseline and in response to relevant stimuli. Finally, the information about the individual angiogenesis/arteriogenesis requirements for each patient will need to be translated into tailored clinical therapies, which may use angiogenic/arteriogenic factors, inhibition of anti-arteriogenic pathways or angiogenic/arteriogenic cells, either in isolation or in combination. The hope is that such individualized approaches can maximize the efficacy and outcome of clinical therapies.

Acknowledgments

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