

Identifying Therapeutic Targets in Cerebrovascular Diseases Using Wholegenome Transcriptomics

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Stroke is a devastating condition afflicting mostly the elderly for which no viable medication exists to improve neurorehabilitation. In particular, great clinical benefit may accrue from deciphering and targeting basic neurobiological mechanisms underlying post-stroke CNS recovery both in structural and functional terms. Studies of stroke in experimental animals have identified a variety of interventions with marked neuroprotective effects, but most of these approaches have failed to benefit aged human stroke victims, perhaps because such therapies have been developed in stroke models using young animals. Indeed, recent studies of experimental stroke in the aged animal reveal age differences that may have more clinical relevance; both for understanding cellular responses to stroke and for identification of beneficial interventions [1]. Yet these studies fail to fully explain the better outcome of young rats, possibly because they investigated only a small number of genetic events.

DNA array technology may provide insight into the mechanisms underlying differences between old and young animals in rate and extent of brain repair and regeneration after stroke. Recently, by using custom macroarrays, we were able to show that expression of genes related to DNA damage, apoptosis and scar formation was increased in aged rats but not or to a significant lesser extent in young rats, while genes involved in neuroprotection and antioxidant defence appeared diminished in aged rats [2]. Other studies of focal cerebral ischemia have identified a series of key molecular events and a number of changes in gene regulation following infarct [3-5]. These studies revealed changes in transcriptional activity of a variety of genes related to stress response, inflammation, acute- and delayed cell death. However, previous studies were done by using arrays with a small number of genes [4,5] or, in one case, with proprietary chips containing 11,000 genes and sequence tags, but at a time when the rat genome was not fully sequenced [3].

Since these early studies, the rat genome has been published [3]. In addition, the recent development of semiautomated pathway analysis tools allows researchers to predict rapidly how changes in gene expression are translated into altered physiological activities. An important omission of these studies is that they did not include aged animals. The importance of animal age in the physiological response to stroke is emphasized by a recent study that identified an age-specific sprouting or regeneration transcriptome that differentially regulates the process of brain reorganization after brain infarct in young vs. aged animals [6]. However, the genomic response to stroke is not limited to the axonal sprouting, but also includes physiologic, metabolic, apoptotic, immunologic, proliferative, developmental, angiogenic and wound healing processes that are of equal importance to neurological rehabilitation. In a study directed at elucidating the role of some of these additional processes, we employed custom DNA arrays containing genes related to hypoxia signalling, DNA damage and apoptosis, cellular response to injury, axonal damage and re-growth, cell differentiation, dendritogenesis and neurogenesis. We showed an age-related unfolding of genetic events in the contralateral, undamaged hemisphere of post-stroke aged rats, which differed from that seen in young animals [2].

Changes in global gene expression provide a quantitative measure of the differences between young and aged animals. For therapeutic

purposes, however, we must identify specific functional pathways associated with the observed genetic changes. These changes may range from physiological responses to stroke to pathways involving tissue regeneration and remodelling.

To date, all mono therapeutic attempts to prevent or lessen brain damage following stroke have failed. In view of our findings that stroke impacts a wide range of systems, from CNS physiology to CNS regeneration and plasticity in an age-dependent manner, the failure of therapies aimed at a single target system is perhaps inevitable. Our results suggest that a multi-stage, multimodal treatment in aged animals may be more likely to produce positive results. While a multi-modal therapeutic approach is promising, one particularly difficult hurdle will be to offset the post-stroke downregulation of genes such as those involved in normal physiology and brain plasticity. This anticipated difficulty stems from the fact that most of the drugs are designed to inhibit gene function whereas for brain recovery of equal importance is to develop drugs that stimulate the expression of genes that are persistently downregulated.

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