Identifying Therapeutic Targets in Cerebrovascular Diseases Using Wholegenome Transcriptomics

Aurel Popa-Wagner* and Ana-Maria Buga

Department of Psychiatry, University of Medicine Rostock, Gehlsheimer Strasse 20, D-18147, Rostock, Germany

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 defense 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 transcriptome provides molecular control of axonal sprouting to brain injury during aging. Ageing Res Rev 10: 71-79.


Chromosomal localization 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 transcriptome provides molecular control of axonal sprouting to brain injury during aging. Ageing Res Rev 10: 71-79.


References


