Defining targets in stroke for future gene therapy

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INTRODUCTION

Stroke is the loss of cerebral function caused by the interruption of the blood supply to the brain that occasions variable symptoms depending on what area is affected. It ranks second as the cause of death worldwide. However, the clinical, social and economic burdens of stroke are not consequence of mortality; they are the result of the large majority of stroke patients who survive but are mentally or physically disabled. For this reason, there have been lots of investments trying to reach an appropriate treatment, but no attempt promises a great opportunity except for rtPA.

AIMS

Few available therapeutic options and numerous failed clinical trials seem to be a contradiction considering the intensive research efforts in this field.

• Review the strategies tested - Analysis of failure in translational settings for preclinical to clinical.

• Evaluate current feasibility of gene therapy.

STROKE AND ISCHEMIC DAMAGE

Transient or permanent reduction of cerebral blood flow (CBF) which is associated with reduction of oxygen distribution (hypoxia), nutrients and elimination of metabolic products causes important impairments at tissue level known as ischemia. This will induce a cascade of secondary effects which is the real cause of death because flux restoration does not prevent from cellular demise.
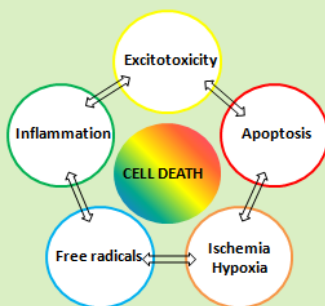
This occlusion will cause changes in microcirculation that will result in variable degrees of hipoperfusion across the ischemic zone. As a consequence, an adjacent area with lesser hipoperfusion is formed, which is called penumbra (brain area which preserves blood flux between functional and morphologic threshold).
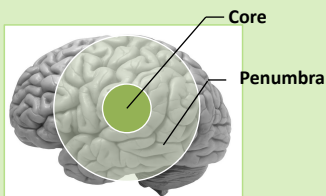
NEUROPROTECTION AND STROKE: Translational failure

Neuroprotection refers to the intensively studied strategies, applied singly or in combination, which try to target the previous molecular events by antagonizing, interrupting or slowing them, especially in penumbra zone. Unfortunately, despite the amount of preclinical studies and clinical trials that have been performed, all attempts in ischemic stroke have failed.

From bench to the bedside: improvements for a suitable translation

• Re-evaluation of pathophysiology and Knowledge extension

• Better animal models (older, with co-morbidities)

• Increase sample size

• Standardize outcome measures

• Multi-stage approach

• Optimize the therapeutic time window, dose and route of administration in humans

NEUROPROTECTION AND GENE THERAPY

On one hand, what is currently known about stroke nature only elicits therapeutic treatment because a preventive approach is not possible. On the other hand, structural and functional recovery is not achieved immediately after treatment; it is required a period of time to restore imbalance. Considering these aspects, gene therapy may be viewed as a good option to treat it, but molecular mechanisms induced by stroke have a quite well established time course which in turn means that the time to act is restricted and limited .

[1]Endres M, Engelhardt B et al. Pathobiology of stroke induced damage, endogenous repair and regeneration.

Neuroprotection		Gene Therapy
Not preventive treatment	✓	Therapeutic treatment
Structural and functional recovery not immediately	✓	Stable long-term expression
Administration in specific moment	✗	Time lag

NEURAL PLASTICITY AND GENE THERAPY

Penumbra is not just passively dying over time but it is also actively recovering; Homeostatic alterations induced by lack of oxygen and nutrients activate a neurorepair and neuroregeneration process (neurogenesis, angiogenesis and sinaptogenesis). Therefore, these mechanisms have been noticed as new strategies because they are much greater than previously thought.

Neural plasticity		Gene Therapy
Structural and functional recovery not immediately	✓	Stable long-term expression
Broader time window	✓	Time lag
Insufficient natural response	✓	Increases/ reinforces expression
Unknowledge of details	✗	knowledge about its regulation and development over time

CONCLUSIONS

Few available therapeutic options and numerous failed clinical trials seem to be a contradiction considering the intensive research efforts in this field. So, it is obvious that this failure demands:

• An examination of pathophysiology of ischemic brain injury

• Changes in methodological process and progresses in gene therapy

• A detailed knowledge about how the processes related to neurogenesis, angiogenesis and sinaptogenesis develop over time and how they are regulated

To sum up, gene therapy is not an ideal option for the neuroprotection approach taking into account previous limitations. By contrast, it could be a suitable future tool by reinforcing neuronal growth if significant steps in knowledge of neuroregeneration were done.

[1]Endres M, Engelhardt B et al. Improving outcome after stroke: Overcoming the translational roadlock. *Cerebrovasc Dis*, 25: 268-278, 2008.