Therapeutic Potential and Possible Risks of Pleiotropic Growth Factors in Ischemic Stroke

To the Editor:

In their meta-analysis, Minnerup and colleagues\(^1\) summarize work on granulocyte-colony stimulating factor (G-CSF) in rat and mouse models of focal cerebral ischemia, concluding that G-CSF based on its survival- and recovery-promoting effects in a total of 13 experimental stroke studies is a confident candidate for stroke treatment. Unlike other neuroprotectants, G-CSF appears to exhibit a particularly long time-window of opportunity, which makes this factor interesting for clinical application.

We shortly hesitated when reading the inclusion strategy for this meta-analysis. As such, one study with deleterious effects of G-CSF\(^2\) was excluded from the database based on the fact that effects of G-CSF were evaluated in a transgenic mouse line. Using the CB-17 mouse, which is a mouse strain used for establishing severe combined immunodeficiency mice,\(^2\) the latter article showed an exacerbation of inflammatory responses, cerebral atrophy and neurological deficits after G-CSF treatment, which is in contrast to all other studies and indeed difficult to interpret. In view of G-CSF representing an anti-inflammatory strategy,\(^1\) stroke itself being followed by an immunodeficient state,\(^3\) the authors should not neglect such single observations, even when rather unusual mouse strains are used.

Pleiotropic molecules have the great advantage of strong and multifaceted actions in the stroke brain. Yet, such compounds particularly should carefully be screened for detrimental actions, because these actions may potentially outweigh the beneficial effects in the clinical setting. The long history of clinical study failures in the stroke field clearly demonstrates the importance of not disregarding undesirable side effects in the experimental setting, because such side effects may represent pitfalls via which a molecule may later on fail in clinics.

Ambiguous effects have previously been shown also for other pleiotropic growth factors with stimulating effect on angiogenesis, i.e., vascular endothelial growth factor, which because of its detrimental effect on brain edema\(^4\) is perhaps not a good candidate for clinical therapy. Based on known data, G-CSF does not appear to promote edema formation in the brain.\(^1\) As such, G-CSF may possibly represent a better candidate molecule. Yet, to ensure the success of ongoing trials, unfavorable actions should not be overlooked.

Disclosures

None.

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