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Advances in Nanomedicine for Treatment of Stroke

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Stroke continues to be the most serious and debilitating neurological disorder in the United States. With a new event every 40 seconds and a victim every 4 minutes, it is the fifth leading cause of death and number one cause of disability. A recent update from the Stroke Statistics Subcommittee of the American Heart Association reported that about 795,000 people in the US experience a new or recurrent stroke each year [1]. Ischemic stroke (blockage of a blood vessel supplying the brain) contributes 80% of the total, and hemorrhagic stroke (bleeding into or around the brain) makes up the rest. National Institutes of Health (NIH) estimate that stroke costs exceed $73 billion in US healthcare dollars per year [2]. Despite the severity of this condition, the only available FDA approved pharmacological treatments for ischemic stroke are: endovascular recanalization therapy and intravenous administration of recombinant tissue plasminogen activator (t-PA), which dissolves the clot and restores blood flow to the brain [3]. The limitation of the endovascular recanalization procedure is 1) only limited population with large vessel occlusions and salvageable brain tissue actually benefits from the therapy; 2) requirement of significant resources in both equipment and trained personnel to perform the surgery [4]. The treatment with t-PA is complicated by: 1) a relatively short "window of opportunity" of only 3-4.5 hours between infarct and treatment; 2) an increased risk for subarachnoid hemorrhage; and 3) neurotoxicity. As a result, only a few patients receive (3-8.5%) and benefit (1-2%) from t-PA treatment. Neither technique addresses cellular damage to brain tissue adjacent to the infracted area, known as the stroke penumbra. More than 1,000 molecules broadly classified as neuroprotective, aiming to stop or slow the secondary damage associated with the ischemic cascade following stroke, have shown promise in the initial stages of research but have failed to demonstrate efficacy in clinical studies because of inadequate efficacy or side effects [5]. A new approach is therefore needed urgently, one which has the potential to address both the restoration of blood flow and attenuation of secondary damage to the penumbral area [5].

Recently, there has been considerable interest in the application of nanomedicine to the treatment of stroke [6-12]. The prime reasons behind their popularity are 1) feasibility of the nanomedicine to decrease neurotoxicity by decreasing the dose; 2) ability to cross the blood brain barrier and ability to accumulate in the ischemic region [13]; 3) target the clot by means of ligand based targeting; 4) release the cargo under specific stimuli [14]. Liposomes have been at the forefront of these investigations followed by polymeric nanoparticles owing to their approval for clinical use, biodegradability and biocompatibility. Other nanocarriers such as platinum [15], ceria [16] and carbon nanotubes [17] have been also investigated for their free radical scavenging properties. Various pharmaceutical actives have been investigated including: thrombolytics [18] such as t-PA [19], streptokinase [20,21] and plasmin [22]; hemoglobin [23-28]; tacrolimus (FK506) [13,29-32]; superoxide dismutase [33]; asialo-erythropoietin [31,34]; IRL-1620 [35]; fasudil [36]; bioactive gases such as nitric oxide [37], Xenon [38]; Nerve Growth Factor (NGF) [39]; citicoline [40,41]; ZL006 [42,43]; antioxidant enzymes [44-46]; luteolin [47]; angiogenic peptides [48] and siRNA [49]. In an animal model of permanent middle cerebral artery occlusion (pMCAO), intravenously-administered 100 nm liposomes [13,29] were found to accumulate in the ischemic core and penumbra region when administered 1-2 hr after occlusion despite reduction in the cerebral blood perfusion as confirmed by fluorescence imaging and positron emission tomography (PET). Liposomes have also been surface modified with polyethylene glycol (PEG) coating to improve their circulation time and to improve their target specificity, by adding moieties such as transfer in receptor [41,43,50,51], Fas ligand antibody [52].

A group of researchers are studying the delivery of medical gasses using echogenic liposomes [19,22,37,38,53-56]. Echogenic liposomes are liposomes that encapsulate both gas and fluid in their phospholipid bilayer and act as contrast agent for ultrasound. Thrombolytics such as t-PA [55] and plasmin [22] have been encapsulated in echogenic liposomes allowing local delivery with minimal systemic exposure. Combination approaches [57,58] such as delivering antioxidant/anti-inflammatory agents with t-PA have been reported to significantly improve the treatment outcomes. Interestingly, however, when an anti-oxidant was encapsulated into and delivered by three different nanocarriers - PEGylated liposomes or polymeric nanoparticles made up of PLA and PLGA with or without targeting moiety– no significant difference was observed in infarct volume reduction [44], indicating the probability that amount of drug encapsulated in the nanocarrier is of greater importance than the choice of nanocarrier or the targeting moiety. Another relatively new area that is gaining interest is in the arena of nano-theranostics [59-61] where diagnosis and therapy is carried out simultaneously using the same nanomedicines. Despite these excellent advances in nanomedicine research that has led to increase in safety and efficacy of neuroprotective and neuroreparative agents that are used in the treatment of stroke, a clinically functioning product is still lacking.

Nanomedicine has great potential in the treatment of stroke. It has been established that nanomedicines can deliver drugs across brain for efficacious reduction in infract volume and reduce the toxicity of treatment with t-PA when compared to conventional delivery systems. Further work, however, is needed in order to translate these advances into improved clinical outcomes. Effective nanocarrier design to improve drug encapsulation and release, rather than targeting, following STAIR guidelines [62] to evaluate efficacy of the nanomedicine in animal models is needed to improve the chances of nanomedicine being developed into a clinically useful treatment for stroke.

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