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An iodine labeled injectable hyaluronic acid hydrogel for an *in vivo* bicolor x-ray monitoring of a biomimetic scaffold in brain regeneration cell therapy

Moustoifa Said^{1,2}, Clément Takavoli^{3,4}, Chloé Dumot⁴, Nora Collomb¹, Anaïck Moisan⁵, Céline Auxenfans⁶, Emmanuel L. Barbier¹, Karine Toupet⁷, Emmanuel Brun³, Hélène Elleaume³, Danièle Noel⁷, Marlène Wiart⁴, Claire Rome¹, Rachel Auzély-Velty², Olivier Detante^{1,8}

¹Univ Grenoble Alpes, Inserm, U1216, Grenoble Institut Neurosciences, Grenoble, France

²Univ. Grenoble Alpes, Centre des Recherches sur les Macromolécules Végétales, CNRS UPR 5301, Grenoble, France

³Univ. Grenoble Alpes, Inserm, UA7 Strobe, Grenoble, France

⁴Univ-Lyon, IRIS team, CarMeN Laboratory, Inserm U1060, INRA U1397, INSA Lyon, Université Claude Bernard Lyon 1, Groupement Hospitalier Est, 59 bd. Pinel, Bron, France

⁵Unité de Thérapie et d'Ingénierie Cellulaire - EFS Rhône Alpes Auvergne, Saint-Ismier, France

⁶Bank of Tissues and Cells, Lyon University Hospital, Lyon, France

⁷Institut for Regenerative Medicine and Biotherapy, UMR 1183, Inserm, Montpellier University, Montpellier, France

⁸Stroke Unit, Department of Neurology, University Hospital of Grenoble, Grenoble, France

moustoifa.said@univ-grenoble-alpes.fr

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INTRODUCTION

Cell transplantation has emerged as a promising regenerative medicine therapy for ischemic stroke by replacing death cells and by stimulating endogenous self-repairing mechanisms¹. Unfortunately, the therapeutic efficacy is compromised by a substantial loss of grafted cells². Injectable hydrogels combined with stem cells have been proposed as a promising strategy to improve cell retention at the infarct site and their survival³. For this purpose, we proposed to use a recently developed hyaluronic acid (HA) hydrogel, that exhibits self-healing and injectability properties, as a biomimetic scaffold for delivery of transplanted cells in the brain lesion⁴. As a combined advanced therapy medicinal product candidate, an *in vivo* follow-up is required to monitor both the fate of the hydrogel scaffold and cells in a long temporal window. In this context, a radiopaque iodinated-labeled HA hydrogel (HA-I) was designed. Then, the tracking of both hydrogel scaffold and gold-labeled human adipose-derived mesenchymal stem cells (Au-hASC) in a specific and quantitative manner was assessed *in vivo* by bicolor imaging using spectral photon-counting computed tomography (SPCCT) and synchrotron K-Edge subtraction computed tomography (KES-CT).

EXPERIMENTAL METHODS

Two modified iodine-labeled hyaluronic acid (HA-I) partners were synthesized by grafting an iodine contrast agent (acetrizic acid, TBA) on functionalized HA chains in mild conditions. The HA-I hydrogel was prepared by simply mixing in physiological conditions these two modified HA-I partners that can self-crosslink *via* boronate ester bond formation. The iodine concentration in HA-I hydrogel was quantified by ICP-MS analysis and KES-CT. Cell viability and proliferation of hASC (0.1 10⁶ hASC/ 200 μ L HA-I hydrogel at day 0) were evaluated in different cell culture periods. *In vivo* intracerebral injections of HA-I hydrogel as a control and Au-hASC embedded within HA-I hydrogel (0.5 10⁶ Au-hASC in 10 μ L HA-I) in healthy rats (n=5) were monitored by magnetic resonance imaging (MRI). Then, on day 4 following the transplantation, bicolor imaging was performed using SPCCT and synchrotron KES-CT.

RESULTS AND DISCUSSION

An iodine-labeled HA hydrogel was formulated in physiological conditions with an iodine concentration [I]=2.4 mg/mL, suitable for X-Ray imaging techniques (Figure 1A). *In vitro* cytotoxicity studies demonstrated a high cell viability after 7 days (> 80 % of cell viability). The dynamic rheological behaviour of the HA-I hydrogel showed that the storage moduli (G') at 25 and 37 °C displayed a plateau in the frequency range

0.01-10 Hz. The G' value (340 Pa, at 1Hz, 25°C) was suitable for a mini-invasive transplantation of Au-hASC in healthy rat brain (Figure 1B). Then, bicolor imaging using a KES-CT 3D reconstruction revealed cell retention of the biomimetic scaffold (Au-hASC embedded within HA-I hydrogel) (Figure 1C).

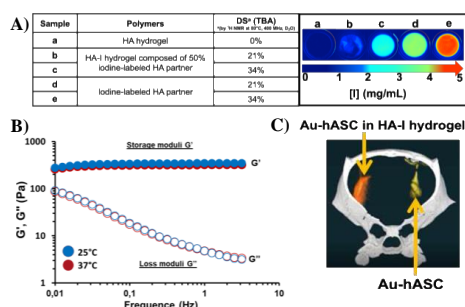


Figure 1: A) Iodine quantifications by KES-CT in HA hydrogels samples B) Dynamic rheological behavior of HA-I hydrogel. C) Ex vivo 3D image of healthy rat brain obtained with KES-CT.

CONCLUSION

A radiopaque iodine-labeled injectable HA hydrogel was successfully developed to deliver Au-hASC in healthy rat brains. Our first results demonstrate the ability to monitor the fate of stem cells on one hand and of cell-embedding hydrogel on the other hand by bicolor imaging using KES-CT. This paves the way for further investigations of this dual-labeled repair kit toward its applicability in cell therapy. One of the perspectives of this work is thus to evaluate its therapeutic effect after intracerebral administration in a rat model of ischemic stroke by coupling multimodal imaging (KES-CT) for monitoring cells and scaffold and advanced multiparametric MRI methods for evaluating tissue repair.

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