ORIGINAL ARTICLE

Fabrication and Characterisations of a Collagen-Based Composite Membrane for HepG2 Cell Attachment

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ABSTRACT

Recent evidence suggests liver cancer cells in the bloodstream (liver CTCs) can be key indicators of liver cancer progression. **Objective:** Hence, the current study aimed to fabricate a porous composite membrane with collagen and to perform its characterisations for liver cancer cell attachment. **Methodology:** A composite membrane was synthesised by solution casting, containing 5 mg/mL graphene oxide (GO), 1 wt% polyvinyl alcohol (PVA), 3 wt% polyethylene glycol (PEG), 1 wt% bioactive glass (BG) and 0.5 wt% Barramundi skin collagen. Its physical, mechanical, chemical, and cytocompatibility properties were characterised. **Results:** The composite membrane achieved an average pore size of 35 µm, confirmed by SEM. It demonstrated favourable mechanical properties for liver cancer cell isolation. FTIR analyses identified functional groups that enhance cell adhesion. The overexpression of CD105 in HepG2 demonstrated that the liver cancer cells effectively attached to the membrane surface with minimal cytotoxicity. **Conclusion:** The composite membrane was developed with an optimal pore size, structure and biocompatibility characteristics, making it promising for liver cancer cells attachment.

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INTRODUCTION

Hepatocellular carcinoma (HCC) has been rising globally. Studies have shown a relation between cancer progression and circulating tumour cells (CTCs). Currently, the CellSearch system is limited to detecting CTCs in prostate, breast, and colorectal cancer patients (1). Recent studies show CD105's significance in liver CTCs during angiogenesis and metastasis (2). Close monitoring of liver cancer cells expressing CD105 in patients would enable early intervention to prevent HCC progression.

Existing research on CTCs has explored graphene and polymeric membranes (3, 4). However, the fabrication employs an electrospinning technique that requires high voltage. Meanwhile, phase inversion uses solvents, making both methods impractical for large-scale production (5).

Two important aspects in membrane fabrication include structural and biocompatibility characteristics. Graphene oxide (GO) has shown promise as a material for fabricating composite membranes to isolate CTCs (3). Polymers such as Polyvinyl alcohol (PVA) are used for film casting, while polyethylene glycol (PEG) acts as a pore-forming agent (6). Furthermore, to enhance membrane biocompatibility, bioactive glass (BG) and collagen were studied for their cell regeneration properties (7, 8). The presence of natural compounds like collagen can stimulate cell growth (9, 10). These features may support liver cancer cell attachment to the

composite membrane.

Studies have demonstrated that bovine collagen-coated substrate can significantly improve the capture efficiency of circulating cancer cells than the traditional culture method. Calf skin collagen was incorporated in a nanotube chip for the isolation of breast cancer cells (11). In another study, bovine collagen was also used in a microfluidic system for testing the viability of fibroblast cells (L929) (12) and to produce a scaffold to maintain HepG2 cell viability as in a tumour microenvironment (13, 14). To date, Barramundi skin collagen has not been tested for the attachment of HepG2 cells in the fabricated composite membrane. This study aimed to fabricate a porous composite membrane with polymers, BG and collagen and perform characterisation for liver cancer cell attachment.

The monitoring of liver cancer has traditionally relied on the AFP (alpha-fetoprotein) test only. However, this biomarker is not always specific to liver cancer and can be influenced by other liver conditions (15). Multiple studies have highlighted the clinical importance of CTCs (16, 17). It will enable early intervention to prevent the progression of cancer. Therefore, employing a sensitive composite membrane will facilitate the detection of liver CTCs and offer valuable insights for hepatocellular carcinoma management in addition to AFP.

MATERIALS AND METHODS

Materials

The materials used for the synthesis of GO were pure graphite powder, sulfuric acid, potassium permanganate, hydrogen peroxide and hydrochloric acid. For the synthesis of BG, the materials comprised of nitric acid, tetraethyl orthosilicate, triethyl phosphate, calcium nitrate tetrahydrate, and sodium nitrate powder. The polymers used were a 3000 Mw PEG solution and 13,000–23,000 Mw PVA from Sigma-Aldrich (Massachusetts, US). Two types of collagens were utilised: commercial marine collagen derived from Tilapia scales from YKL Multi Sdn. Bhd., Malaysia, and acid-soluble Barramundi skin collagen obtained from the Department of Chemical and Environmental Engineering, University of Technology Malaysia (UTM). For biological characterisations, reagents were Penicillin-Streptomycin Mixed Solution (Stabilised) from Nacalai Tesque, Tokyo, Japan, foetal bovine serum (FBS) from Tico Europe, Amstelveen, Netherlands, and Eagle's Minimum Essential Medium (EMEM) from ATCC, Manassas, United States. Cell lines used were the HepG2/C3A human hepatocellular carcinoma cell line and L929 fibroblast cell line purchased from the American Tissue Culture Collection (ATCC). Cell viability utilised Calcein AM stain from Sigma-Aldrich (Massachusetts, US). Immunofluorescence analysis utilised CD105 antibody purchased from BD Biosciences (New Jersey, US) and mounting medium with DAPI was from Vector (Burlingame, California).

Fabrication of Composite Membrane

To ensure the reproducibility of the fabricated membrane, the temperature of casting, the concentration of the GO, polymers and biomaterials had been optimised to achieve the size of approximately 40 µm for size-based isolation of liver cancer HepG2 cells. The optimal concentration of each component is provided below:
The membrane was fabricated with some modifications of previous studies (18, 19). In brief, BG powder (1 wt%) was mixed with 5 mg/mL GO powder in 10 mL Milli-Q water and sonicated with the POWERSONIC 405 (Daegu, South Korea) for 2 hours. It was followed by centrifugation at 4,000 rpm for 30 minutes. Consequently, the supernatant was mixed with 1 wt% PVA, 3 wt% PEG, and 0.5 wt% collagen. The solution was heated at 90°C for 15 minutes and stirred overnight. After stirring, 10 ml of the membrane solution was poured into a mould (6 cm-diameter) and left to dry at 25°C for three days. After drying, the membrane was stored in a container at room temperature. It was UV sterilised prior to use.

Scanning Electron Microscopy (SEM)

SEM (Quanta FEG 650) was performed to measure pore size and observe the cross-section of the fabricated membranes (20).

Mechanical Strength Tests

Tensile and burst tests were conducted to determine the membrane's strength using Gotech AI-3000-U and GT-7013-ADP (Gotech, Taichung City, Taiwan). In the tensile test, the composite membrane (80 mm x 20 mm) was pulled until it tore between two grippers to measure pulling force against length changes (21). Meanwhile, in the burst test, the membrane's burst pressure (100 mm x 100 mm) was measured under hydraulic pressure at the rupture point (22).

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR was performed with FT-NIR analyser (PerkinElmer, Connecticut, United States) to identify functional groups, between 4,000 and 600 cm^{-1} at a resolution of 4, a data interval of 1 cm^{-1}, and 32 scans (20).

Expression of CD105 by Immunofluorescence Method

Analysis of CD105 expression was performed in liver cancer cells (HepG2) and fibroblast cells (L929). Both cells were purchased from American Type Culture Collection (ATCC). The composite membrane (6 mm) was UV-treated for an hour and placed in a 96-well plate. After washing in phosphate buffer saline (PBS),

100 µL of EMEM medium was added and incubated overnight. Subsequently, 2.5 x 10^3 cells were seeded onto the membrane. After three hours, it was washed again and fixed with paraformaldehyde for 30 minutes. Then, it was permeabilized in 0.3% Triton X-100 followed by blocking with 1% BSA in PBS-Tween 20 (PBST) for 30 minutes. The CD105 primary antibody was added and incubated at 4°C for 24 hours. After washing, secondary antibody (goat anti-mouse IgG) was added for another hour at room temperature. Cells were fixed with DAPI stain, and images were captured under a fluorescence microscope (Olympus BX51, Tokyo, Japan) (23). Only viable cells with intact membranes and active metabolism were capable to attach to the membrane.

RESULTS

Scanning Electron Microscopy (SEM)

Both membranes appeared white-yellowish, with the white colour attributed to BG and yellow from collagen (Fig. 1A and 1D). The membrane fabricated from ASC-derived Barramundi skin collagen was smoother and more transparent than commercial collagen. SEM results revealed that the ASC-derived collagen membrane had a composite structure with dense and porous layers with an average pore size of 35 µm (Fig. 1B and 1C), while the commercial collagen membrane was dense and non-porous (Fig. 1E and 1F). Thus, the ASC-derived collagen membrane (composite membrane) was selected for further characterisation.

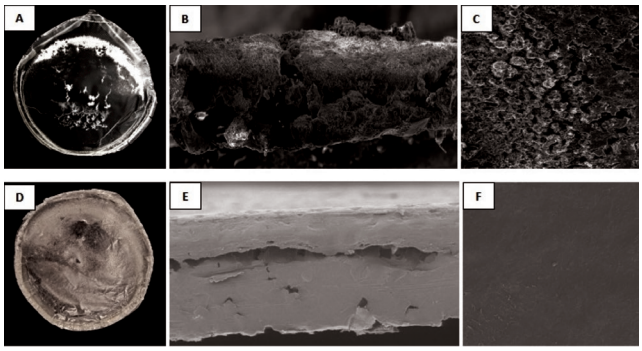

Figure 1: The image and SEM analysis of the cross-section and surface of the Barramundi skin collagen membrane (A, B and C) and the commercial collagen membrane (D, E and F).

Mechanical Strength Tests

The tensile test showed a maximum load of 7.665 N, a tensile strength of 3.484 MPa, and a modulus of 374.035 MPa, with elongation of 2.165% before breaking (Table I). The burst test indicated an average burst strength of 193.1 kPa.

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR analysis confirmed the presence of functional groups on the ASC-derived collagen membrane (Table II). A broad band around 3275 cm^{-o} was associated with O-H bonds from GO-PVA-PEG and N-H stretching from collagen. Amide II and III bands were identified at 1451.99 cm^{-1}, 1555.80 cm^{-1}, and 1264.06 cm^{-1} in collagen. Amide I, associated with C=O stretching, was observed at 1641.32 cm^{-1}.

Alkane (sp C-H) bands at 2862.03 cm^{-1} and 2930.07 cm^{-1} were attributed to GO, PVA, and PEG in the membrane. The C-C stretching and C=O bands appeared at 824.47 cm^{-1} and 1716.07–1734.73 cm^{-1}, respectively. GO and PVA also contributed to alkene (C=C) groups, while C-O or C-OH bonds were detected at 1051.03–1088.39 cm^{-1} in all materials except BG, which showed Si-O-Si and P-O bands at 1200.5 cm^{-1}, 912.65 cm^{-1}, and 1264.08 cm^{-1}.

Immunofluorescence Staining

Immunofluorescence staining showed significant expression of CD105 in HepG2 (25.6 ± 9.1 std), whereas L929 cells did not express CD105 ($p < 0.05$) (Fig. 2)

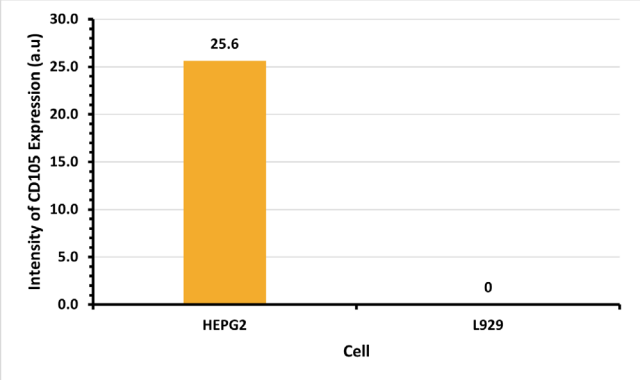

Figure 2: The intensity of CD105 expression in HepG2 (25.6 a.u. ± 9.1) and L929 cells (0.0 a.u.) on the Barramundi skin collagen membrane.

DISCUSSION

The FDA has approved the CellSearch system for monitoring response to treatment in breast, colorectal and prostate cancer patients (24, 25). Since chemotherapy alone may not fully eradicate the disease, CTCs with size range of between 25–40 µm may remain in the bloodstream (3, 26). The chemo-drug resistant cancer cells can metastasise and potentially give rise to secondary tumours at new sites. By employing a minimally invasive method to isolate liver CTCs with the fabricated composite membrane along with the AFP test, this may aid in monitoring of treatment outcome.

The membranes fabricated from different collagen demonstrated physical changes. The ASC-derived collagen from Barramundi had a sponge-like characteristic, which promoted pore formation. In contrast, commercial collagen was in powder form and led to a solid texture without pores. According to a previous report, pores can help promote better cell attachment on membranes (27). Hence, Barramundi

Table I: The mechanical analysis of the composite membrane.

Tensile Test							Bursting test
Thickness (mm)	Width (mm)	Specimen area (mm2)	Maximum load (N)	Tensile strength (MPa)	Tensile Modulus (MPa)	Elongation at Break (%)	Bursting Strength (kPa)
0.11	20	2.2	7.665	3.484	374.035	2.615	193.1

Table II: The FTIR analysis of materials used in composite membrane fabrication.

Bond	Wavelength (cm^{-1})					
	GO	PVA	PEG	BG	Collagen	Membrane
O-H	3228.98 (s)	3323.00 (m)	3368.96 (s)	-	-	3275.84 (s), 2497.60 (m)
N-H	-	-	-	-	3290.70 (m)	3275.84 (s)
Amide II	-	-	-	-	1452.25 (m), 1545.46 (s)	1451.99 (m), 1555.80 (m)
Amide III	-	-	-	-	1238.05 (m)	1264.06 (m)
sp^3 C-H	-	2917.00 – 2984.46 (m)	2903.41 (m)	-	2939.65 (w)	2862.03 (m), 2930.07 (m)
C=C	1617.50 (m)	1541.9 (w)	-	-	-	1699.88 (w)
C-C	810.78 (m)	857.3 (s)	839.03 (m)	-	-	824.47 (s)
C=O	1702.50 (w)	1059.6 (s)	1643.85 (m)	-	1634.28 (s)	1641.32 (m), 1716.07 – 1734.73 (w)
C-O / C-OH	1399.50 (w) – 1078.96 (s)	1143.50 (w)	1084.31 (w)	1240 – 1500 (m)	-	1051.03 – 1088.39 (s)
Si-O-Si	-	-	-	1248.8 (m)	-	1200.5 (m)
P-O	-	-	-	918.5 – 1009.5 (s)	-	912.65, 1264.08 (s)

skin collagen composite membrane was selected for further characterisation.

Analysis on the Barramundi skin collagen composite membrane demonstrated favourable mechanical strength. All materials contributed to the strength, but PEG might weaken the membrane by creating pores (28). Generally, higher tensile strength correlates with greater burst strength, but porosity may limit its overall strength. However, the strength might be sufficient to withstand filtration pressure.

Additionally, the presence of hydroxyl, amino, carbonyl, and carboxyl groups on the ASC-derived collagen composite membrane promotes hydrogen bonding with cell surface molecules, thus enhancing cell adhesion. These functional groups may improve the hydrophilicity of the composite membrane through strong interactions with water (29). Since cell membranes are naturally hydrophilic, they will bind to the hydrophilic sites of the composite membrane.

The FTIR result (Table II) showed more positively charged amino groups, alkene groups, and C-S functional groups than negatively charged (carboxyl, hydroxyl, Si-O-Si and P-O functional groups) and neutral functional groups (alkanes and carbonyl groups). This causes the composite membrane to be positively charged. Consequently, it attracts liver cancer cells (HepG2), which are more negatively charged than fibroblasts due to the abundance of phospholipids in cancer cell membranes (30).

Recent insights into the use of membrane-bound Hsp70 as a biomarker for CTC isolation have indicated that graphite can serve as an effective substrate for this purpose, capitalizing on the higher expression of Hsp70 on the surface of CTCs compared to normal cells (31, 32). Additionally, Zhu et al. have explored the combination of polymeric nanoparticles with magnetic properties, enabling a dual-purpose system for both isolation and signalling detection of CTCs during magnetic resonance imaging (33).

Primary liver tumour, particularly hepatocellular carcinoma does highly expresses CD105 as reported previously (34-36). Contrarily, liver infection markers are primarily detected through liver function tests (LFTs). The detection is based on the amount of alkaline transaminase (ALT), aspartate transaminase (AST) and alkaline phosphatase (ALP). These markers are detected by the spectrophotometry method which differs from CTCs detection.

Further characterisation by immunofluorescence confirmed CD105 expression in viable HepG2. The composite membrane interaction with CD105-expressing liver cancer cells may enhance the specificity of isolating CTCs from cancer patients' blood, thus offering valuable opportunities for prognostic applications. This finding suggested that the membrane was biocompatible to allow efficient liver cancer cell attachment and viability for up to three hours.

CONCLUSION

The fabricated composite membrane achieved optimal characteristics through the presence of additional positively charged functional groups, which enhanced hydrophilicity for liver cancer cell attachment. The membrane exhibited favourable mechanical strength and demonstrated cell specificity, as liver cancer cells adhered more effectively than fibroblast cells. The composite membrane can be developed into a syringe adapter. The placement of the adapter at the syringe hub will enable filtration of serum and detection of CTCs. It can aid in real-time monitoring of liver CTCs in liver cancer patients. Further studies are warranted to evaluate its potential applications in CTC monitoring.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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