ABSTRACT SECTION

1. The effect of mesenchymal stem cell conditioned media on corneal stromal fibroblast wound healing activities

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Abstract

Aims To investigate the effects of conditioned media from mesenchymal stem cells (MSC) on the wound healing activities of corneal stromal fibroblasts.

Methods Cell cycle analysis and early stage activation of apoptosis, chemotactic chambers and fibroblast-populated type I collagen gels were used to assess corneal stromal fibroblast proliferation, migration and contraction, respectively. Fibroblasts were obtained from human donor corneas and MSC from fresh rat bone marrow. MSC conditioned media and fibroblast culture medium (FCM), with and without calf serum supplementation, were compared.

Results MSC conditioned media and serum-free FCM had an inhibitory effect on the progression of corneal fibroblasts through the cell cycle. There was a significant increase in the number of cells in the G0–G1 phase for MSC conditioned media and serum-free FCM (p=0.001, p=0.97 respectively).

Fibroblast migration and relaxed and stressed gel contraction were significantly inhibited by MSC conditioned media and serum-free FCM compared with FCM with serum (all p=0.001). Glucose and lactate analysis confirmed that these factors were not contributing to this effect.

Conclusion MSC conditioned media was found to inhibit the wound healing activities of corneal stromal fibroblasts in vitro. Putative factors secreted by MSC could be developed for therapeutic use in corneal repair.

2. Long-term visual and anatomical outcomes following anti-VEGF monotherapy for retinal angiomatous proliferation

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Abstract

Aim To study the long-term visual and anatomical outcomes of antivascular endothelial growth factor (VEGF)

monotherapy for the treatment of patients with retinal angiomatous proliferation (RAP).

Methods Retrospective review of patients who were diagnosed as having AMD and RAP lesions, and who received anti-VEGF injections as the only mode of therapy.

Results 20 eyes (15 patients; nine women, six men) with RAP lesions treated by anti-VEGF were encountered. The mean patient age was 85.8 years (SD±4.54). Nine eyes were treated with intravitreal ranibizumab alone, eight eyes were treated with bevacizumab alone, and three eyes received both drugs. At 1, 3 and 6 months' follow-up the median VA had improved from baseline (20/72) to 20/52 (range: 20/25 to 20/400), 20/45 (range 20/20 to 20/400), and 20/56 (range 20/20 to 20/400), respectively, ($p>0.001$, $p=0.001$ and $p=0.05$, respectively). At the 24-month follow-up, the improvement in VA, defined as a halving of the visual angle, occurred in 37.5% of the cases.

Conclusions Anti-VEGF monotherapy represents a useful treatment option for RAP, with stable or improved visual acuity in 62.5% of patients at 2 years. 25% of eyes required only a single injection, but in most cases (75%) repeated treatments were required, highlighting the need for long term follow-up. Although, in this small study, the results for visual improvement were not statistically significant beyond 3 months, our findings warrant further large-scale investigation.

3. A phase I study of the safety and pharmacokinetics of the histone deacetylase inhibitor belinostat administered in combination with carboplatin and/or paclitaxel in patients with solid tumours

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Abstract

Background: This phase I study assessed the maximum tolerated dose, dose-limiting toxicity (DLT) and pharmacokinetics of belinostat with carboplatin and paclitaxel and the anti-tumour activity of the combination in solid tumours.

Methods: Cohorts of three to six patients were treated with escalating doses of belinostat administered intravenously once daily, days 1–5 q21 days; on day 3, carboplatin (area under the curve (AUC X 5) and/or paclitaxel (175 mg/m^2) were administered 2–3 h after the end of the belinostat infusion.

Results: In all 23 patients received 600–1000 mg/m^2 per day of belinostat with carboplatin and/or paclitaxel. No DLT was observed. The maximal administered dose of belinostat

was 1000 mg/m^2 per day for days 1–5, with paclitaxel (175 mg/m^2) and carboplatin AUC 5 administered on day 3. Grade III/IV adverse events were (*n*; %): leucopenia (5; 22%), neutropenia (7; 30%), thrombocytopenia (3; 13%) anaemia (1; 4%), peripheral sensory neuropathy (*2;* 9%), fatigue (1; 4%), vomiting (1; 4%) and myalgia (1; 4%). The pharmacokinetics of belinostat, paclitaxel and carboplatin were unaltered by the concurrent administration. There were two partial responses (one rectal cancer and one pancreatic cancer). A third patient (mixed mullerian tumour of ovarian origin) showed a complete CA-125 response. In addition, six patients showed a stable disease lasting ⩾ 6 months.

Conclusion: The combination was well tolerated, with no evidence of pharmacokinetic interaction. Further evaluation of anti-tumour activity is warranted.

Keywords: HDAC; belinostat; carboplatin; paclitaxel; BelCaP

4. Placental growth factor (PlGF) enhances breast cancer cell motility by mobilising ERK1/2 phosphorylation and cytoskeletal rearrangement

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Abstract

Background: During metastasis, cancer cells migrate away from the primary tumour and invade the circulatory system and distal tissues. The stimulatory effect of growth factors has been implicated in the migration process. Placental growth factor (PlGF), expressed by 30–50% of primary breast cancers, stimulates measurable breast cancer cell motility *in vitro* within 3 h. This implies that PlGF activates intracellular signalling kinases and cytoskeletal remodelling necessary for cellular migration. The PlGF-mediated motility is prevented by an Flt-1-antagonising peptide, BP-1, and anti-PlGF antibody. The purpose of this study was to determine the intracellular effects of PlGF and the inhibiting peptide, BP-1.

Methods: Anti-PlGF receptor (anti-Flt-1) antibody and inhibitors of intracellular kinases were used for analysis of PlGF-delivered intracellular signals that result in motility. The effects of PlGF and BP-1 on kinase activation, intermediate filament (IF) protein stability, and the actin cytoskeleton were determined by immunohistochemistry, cellular migration assays, and immunoblots.

Results: Placental growth factor stimulated phosphorylation of extracellular-regulated kinase (ERK)1/2 (pERK) in breast cancer cell lines that also increased motility. In the presence of PlGF, BP-1 decreased cellular motility, reversed ERK1/2 phosphorylation, and decreased nuclear and peripheral pERK1/2. ERK1/2 kinases are associated with rearrangements of the actin and IF components of the cellular cytoskeleton. The PlGF caused rearrangements of the actin cytoskeleton, which were blocked by BP-1. The PlGF also stabilised cytokeratin 19 and vimentin expression in MDA-MB-231 human breast cancer cells in the absence of *de novo* transcription and translation.

Conclusions: The PlGF activates ERK1/2 kinases, which are associated with cellular motility, in breast cancer cells. Several of these activating events are blocked by BP-1, which may explain its anti-tumour activity.

Keywords: PlGF; breast cancer; motility; BP-1 peptide; Flt-1; IF protein