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# BPC 157 Promotes Skeletal Muscle Cells Migration in Association with Up-regulation of Paxillin and Vinculin Expression

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BPC 157 was first isolated from human gastric juice. It is a stable 15-amino acid fragment (GEPPPGKPADDAGLV), and the healing-promoting effects of BPC 157 have been reported on muscle injury. The aim of this study was to investigate the effect and molecular mechanism of BPC 157 on migration of skeletal muscle cells.

Skeletal muscle cells were isolated from the gastrocnemius muscle of Sprague–Dawley rats, and treated with BPC 157. The cell migration was evaluated by transwell filter migration assay. The spreading of cells was evaluated microscopically. The protein expressions of paxillin and vinculin (which were positive regulators of cell migration) were assessed by Western blot analysis. The results revealed that BPC 157 could enhance migration and spreading of skeletal muscle cells. Meanwhile, the expression of paxillin and vinculin were up-regulated. It was concluded that BPC 157 promoting migration and spreading of skeletal muscle cells were associated with up-regulation of proteins expression of paxillin and vinculin. (Tw J Phys Med Rehabil 2019; 47(1): 21 - 29)

**Key Words:** BPC 157, skeletal muscle, cell migration

## INTRODUCTION

Muscle injuries are very common among athletic populations, representing 10% to 55% of all acute sports injuries.<sup>[1]</sup> Strains or contusions account for most of acute muscle injuries,<sup>[2]</sup> while laceration and rhabdomyolysis are less common. Muscle injuries not only result in lost

training time and/or competition participation, but subsequent re-injury are often more severe, requiring prolonged rehabilitation.<sup>[3]</sup> Since spontaneous healing of skeletal muscle has been well documented,<sup>[4]</sup> current treatment concept places emphasis on conservative treatment and individualized rehabilitation. However, patients do not respond well to conservative treatment resulting in protracted recovery period, and those who

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return to play has a high risk for relapse.<sup>[5]</sup> A treatment that facilitates regeneration of skeletal muscle is therefore needed.

Various growth factors such as insulin-like growth factor-1 (IGF-1), hepatocyte growth factor (HGF), and vascular endothelial growth factor (VEGF) have shown positive results for skeletal muscle healing in animal models.<sup>[6]</sup> However, the relatively short half-lives of these molecules severely limit their efficacy. BPC 157 is a stable peptide chain consisting of 15 amino acids. Like growth factors, BPC 157 has been shown to promote healing of various tissue injuries, including tendon, ligament, muscle and bone.<sup>[7]</sup> Animal studies have suggested that BPC-157 improves skeletal muscle regeneration after injury.<sup>[8-10]</sup> However, the exact mechanism in which BPC 157 facilitates skeletal muscle healing process remains poorly understood.

Skeletal muscle healing processes can be divided into destruction, repair, and remodeling phase, each with distinct but overlapping cellular reactions. In the repair phase, satellite cells proliferate and differentiate into myoblasts, which then fuse with disrupted muscle fibers.<sup>[11]</sup> Satellite cells normally reside under the basal lamina, upon activation by trauma, they must relocate to the area of damage. This migratory capability of myogenic precursor cells is crucial, as previous studies have shown that direct injection of myoblasts only results in regeneration very close to the injection site.<sup>[12]</sup> Attempts have been made to improve skeletal muscle cell migration, with varying success.<sup>[13,14]</sup>

Paxillin is a 68-kDa cytoskeletal protein, and the main component of focal adhesions (FAs), triggered by the interaction of integrins and extracellular matrix (ECM).<sup>[15]</sup> Associated with focal adhesion kinase (FAK), paxillin functions in transmitting signals downstream of integrins and controls important biological events including cell migration, proliferation, and survival. Paxillin is also tyrosine phosphorylated in response to integrin-mediated cell adhesion and can be phosphorylated by FAK.<sup>[16]</sup> Our earlier work showed that BPC 157 promotes *in vitro* tendon cell resilience and migration via FAK-paxillin pathway.<sup>[17]</sup> This study aims to investigate the mechanism of BPC 157-mediated skeletal muscle healing. We hypothesize that BPC 157 increases skeletal muscle cell vitality and migration,

through modulation of membrane adhesion proteins paxillin and vinculin.

## MATERIALS AND METHODS

### Primary culture of rat gastrocnemius muscle cells

The gastrocnemius muscle was excised from SD rats (weighing 200–250 g) which provided by Bio-Lasco Taiwan Co., Ltd. Rats were sacrificed by inhalation of carbon dioxide, and the gastrocnemius muscle was immediately excised. The surrounding fascia and adipose tissue were removed and muscle was cut and mince into smooth pulp. The minced muscle tissues were treated by 0.2% collagenase type I in TESCA buffer (50mM TES, 0.36mM CaCl<sub>2</sub>) (Sigma–Aldrich, St.Louis, MO), and incubated for 45 min at 37°C in a humidified atmosphere of 5% CO<sub>2</sub>/95% air. Then, tissues were treated with 0.25% trypsin-EDTA (Gibco, Thermo Fisher Scientific, Waltham, MA) and were incubated for another 45 min. After centrifuged with 1000g for 5 min, cell pellets were re-suspended with Dulbecco's modified Eagle's medium (DMEM) (Gibco, Thermo Fisher Scientific, Waltham, MA, USA), with 10% fetal bovine serum (FBS) (Gibco, Thermo Fisher Scientific), 5% chick embryo extract (Gibco, Thermo Fisher Scientific), 100U/ml penicillin, and 100g/ml streptomycin. After 1 h for fibroblast-shaped cells adhering to the plate, the non-adherent cells were transferred to another plate for further sub-culture and were incubated at 37°C in a humidified atmosphere of 5% CO<sub>2</sub>/95% air. After incubation for 24 h, the supernatant (containing skeletal muscle cells) was centrifuged with 01000g for 5 min. The cell pellets were resuspended and cultured in a 10 cm culture plate with DMEM with 10% FBS, 5% chick embryo extract. These cells were used for the following experiment.

### Cell viability test

Skeletal muscle cells were treated or untreated with BPC157 at different concentrations (0.1µg/ml, 0.5 µg/ml, 1 µg/ml, 2 µg/ml BPC157) for 24 h, and the viability of the cells was measured by MTT test.

(3-[4,5-Dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) (Sigma-Aldrich, St. Louis, MI, USA). MTT

reagent (50 µg/ml) was added and incubated at 37°C for 1 hour. The MTT solution was discarded and 1 ml dimethyl sulfoxide (DMSO) was added to dissolve formazan crystals. Aliquots were transferred to the plate of 96 well and detected immediately at 595 nm in a multi-well spectrophotometer, VICTORTM X3 (PerkinElmer Inc., Waltham, MA, USA). This experiment and the following experiments were performed in triplicate (n = 3).

### Transwell filter migration assay

Skeletal muscle cells were treated or untreated with BPC157 at different concentrations (1 µg/ml, 2 µg/ml BPC157) for 24 h, and the cells were seeded at a density of  $1 \times 10^5$  cells per filter. Trans well filters (Costar, Corning, Cambridge, MA, USA) with 8.0 µm pores were used for the migration assay. The inner chamber was filled with 200 µl serum free DMEM and the outer chamber was filled with 600 µl DMEM with 20% FBS. Cells were allowed to migrate for 3 h at 37°C in an atmosphere of 95% air/5% CO<sub>2</sub>. The cells were stained with Liu's stain and then washed twice in PBS. Cells on the upper surface of the filter were removed using a cotton swab. Cells on the lower surface of the filter were counted under eight random fields (HPF)(100x) per filter and the mean number of migrating cells calculated for each concentration. The experiment was performed in triplicate (n = 3).

### Cell Spreading Assay

Skeletal muscle cells were treated or untreated with BPC157 at different concentrations (0.1 µg/ml, 0.5 µg/ml, 1 µg/ml, 2 µg/ml BPC157) for 24 h and subcultured and plated on 6-cm culture dishes with culture medium containing BPC157 at different concentrations. After plating for 30 min, cells were observed under the light microscope (100x and 200x) and photographed. Under this condition, cells generally start to adhere onto the plate within 10 min and then spread out. Cells that remained round and with a much brighter appearance were considered as non-spread cells. Those with pseudopodia extensions were considered as spreading cells. The pseudopodia extensions of spread cells were clearly observed at 200x. Percentages of spread cells per filed were calculated. Three fields were randomly selected for observation.

### Western blot analysis

Cell extracts were prepared in a lysis buffer containing 20mM HEPES, 1mM EDTA, 1mM EGTA, 20mM NaF, 1mM Na<sub>3</sub>VO<sub>4</sub>, 1mM Na<sub>2</sub>P<sub>2</sub>O<sub>7</sub>, 1mM DTT, 0.5mM PMSF, 1 µg/ml leupeptin and 1% Triton X-100. The protein concentration of the cell extracts was determined by Bradford assay (Bio-Rad Laboratories, Richmond, CA, USA). Samples with identical protein quantities were separated by 10 % sodium dodecyl sulfate polyacrylamide gel electrophoresis, and transferred onto a PVDF membrane. The membranes were incubated at room temperature in blocking solution (5 % BSA in TBST) for 1h, followed by 2 h incubation in blocking solution containing an appropriate dilution of primary antibody, e.g. Tubulin (Thermo Fisher Scientific, Waltham, MA, USA), anti-phospho-paxillin (Y118) (Cell Signaling Technology, Danvers, MA, USA), anti-paxillin (Cell Signaling Technology, Danvers, MA, USA). After washing, the membranes were incubated in TBS containing anti-mouse IgG conjugated with horseradish peroxidase (Leinco Technologies, Inc., St. Louis, MI, USA) or anti-rabbit IgG conjugated with horseradish peroxidase (Cell Signaling Technology, Danvers, MA, USA) for 1 h. The membranes were washed three times in TBST and developed with Luminata Crescendo Western HRP substrate (Merck Millipore, Darmstadt, Germany).

### Statistical analysis

All data were expressed as mean  $\pm$  standard error of mean (S.E.M). The Kruskal-Wallis test was used to comparisons between groups. A Mann-Whitney test was used to identify where the difference occurred. The level of statistical significance was set at a p value less than 0.05.

## RESULTS

### BPC157 had no impact on the number of viable skeletal muscle cells

In order to investigate whether BPC157 altered cell proliferation, skeletal muscle cells were treated with different concentrations of BPC157 for 24 h, and MTT assay was used to determine the cell viability. The result

indicated there was no significant difference between different concentrations of BPC157-treated skeletal muscle cells. The relative viable cells of control were  $100.0 \pm 5.3\%$ ,  $95.0 \pm 4.2\%$ ,  $93.6 \pm 3.3\%$ ,  $93.4 \pm 6.0\%$  and  $90.6$

$\pm 2.7\%$  in the control,  $0.1 \mu\text{g/ml}$ ,  $0.5 \mu\text{g/ml}$ ,  $1 \mu\text{g/ml}$ ,  $2 \mu\text{g/ml}$  of BPC157, respectively (Figure 1).

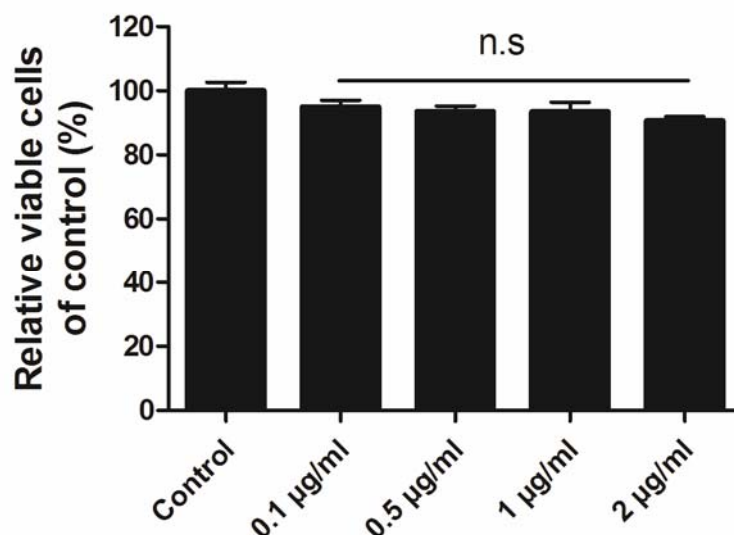


Figure 1. BPC157 had minor effect on cell proliferation. Skeletal muscle cells were treated with  $0.1 \mu\text{g/ml}$ ,  $0.5 \mu\text{g/ml}$ ,  $1 \mu\text{g/ml}$ ,  $2 \mu\text{g/ml}$  BPC157 for 24 h and cell viability was determined by the MTT assay. Data were presented as mean  $\pm$  SEM of three independent experiments (\* $p < 0.05$ )

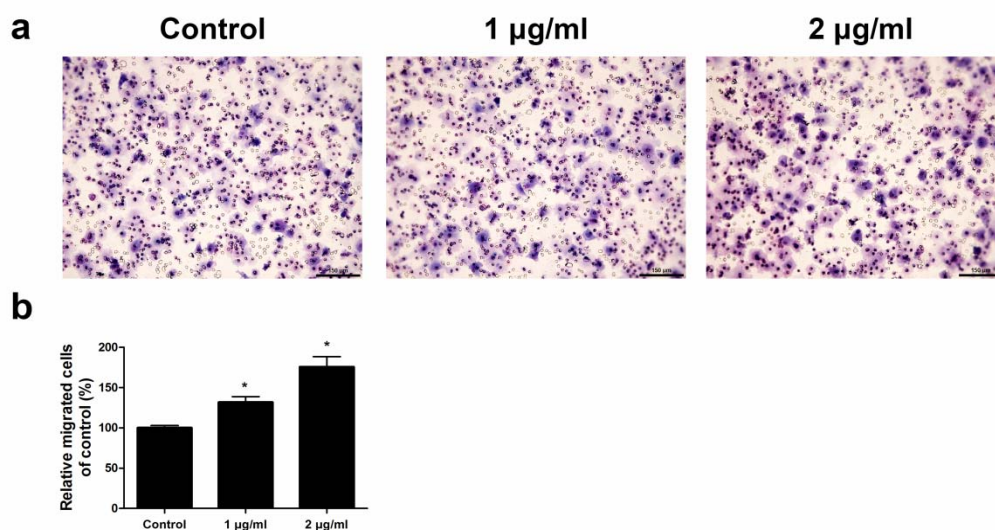


Figure 2. BPC157 increased migrate ability of skeletal muscle cells. Skeletal muscle cells were untreated or treated with  $1 \mu\text{g/ml}$  and  $2 \mu\text{g/ml}$  BPC157 for 24 h. The cell migration was assessed by transwell filter migration assay. The cells migrating across the filter were showed in (a). The relative percentage of migrated cell was shown in (b). Data were presented as mean  $\pm$  SEM of three independent experiments (\* $p < 0.05$ )

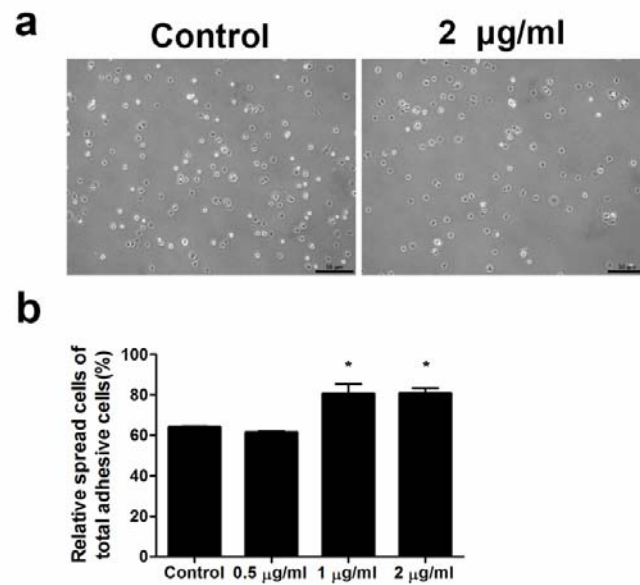


Figure 3. BPC 157 induced spreading of skeletal muscle cells. Skeletal muscle cells were untreated or treated with 0.5 µg/ml, 1 µg/ml and 2 µg/ml BPC157 for 24 h and plated on culture dishes. The numbers of spreading cells were increased by BPC 157 (a). The percentage of spreading cells to adhesion cells was increased after BPC 157 treatment (b). Data were presented as mean±SEM of three independent experiments (\* $p < 0.05$ )

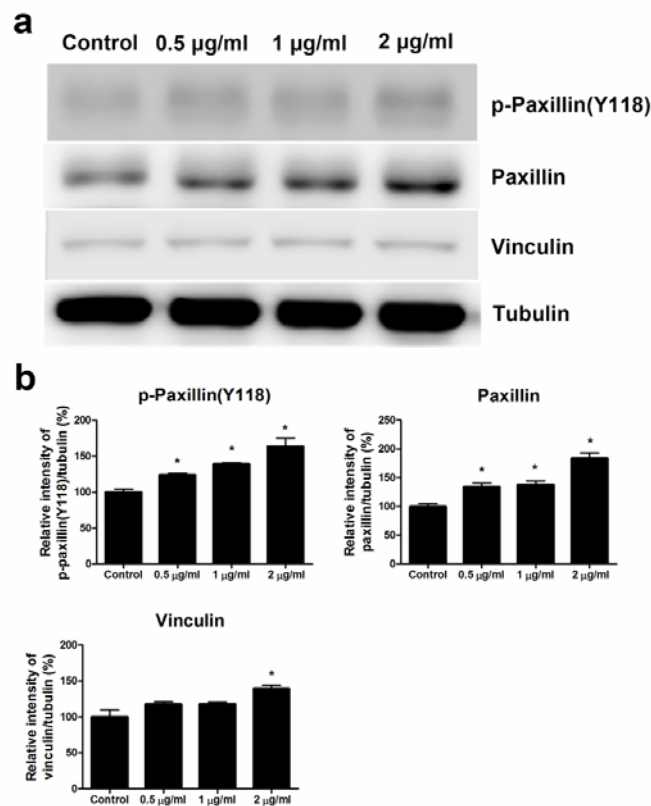


Figure 4. BPC157 induced the expression of paxillin and vinculin in skeletal muscle cells. Skeletal muscle cells were treated with 0.5 µg/ml, 1 µg/ml, 2 µg/ml BPC157 for 24 h. The protein expression in the cell extracts was analyzed by western blotting. Tubulin was used as an internal control (a). The relative band intensities of phospho-paxillin, paxillin and vinculin were shown in (b). Data were presented as mean±SEM of three independent experiments (\* $p < 0.05$ )

### BPC157 induced cell migration of skeletal muscle cells

Skeletal muscle cells were treated with different concentrations of BPC157 for 24 h. The result of migration assay demonstrated that BPC157 dose-dependently induced the cell migration of skeletal muscle cells (Figure 2a). The relative migrated cell rates were  $100 \pm 2.8\%$ ,  $131.7 \pm 7.2\%$ , and  $175.8 \pm 12.8\%$  in the control, 1  $\mu\text{g/ml}$  and 2  $\mu\text{g/ml}$  group, respectively ( $p < 0.05$ , Figure 2b).

### BPC157 promoted cell spreading of skeletal muscle cells

Cell attachment and spreading occur in the initial phase during cell migration process. We used cell spreading assay to examine the appearance of pseudopodia extension. The result showed cell spreading rate was enhanced by BPC 157 (Figure 3a). The relative spread cell rates were  $64.1 \pm 0.4\%$ ,  $61.5 \pm 0.6\%$ ,  $80.5 \pm 4.9\%$  and  $80.8 \pm 2.4\%$  in the control, 0.5  $\mu\text{g/ml}$ , 1  $\mu\text{g/ml}$  and 2  $\mu\text{g/ml}$  group, respectively ( $p < 0.05$ , Figure 3b).

### BPC 157 increased migration-associated protein expression of skeletal muscle cells

Skeletal muscle cells were treated with 0.5  $\mu\text{g/ml}$ , 1  $\mu\text{g/ml}$ , 2  $\mu\text{g/ml}$  BPC 157 for 24 h. The protein extracts of skeletal muscle cells were analyzed by Western blot analysis. Protein expressions of phospho paxillin and paxillin were up-regulated by BPC 157 treatment in a dose-dependent manner, and high concentration (2  $\mu\text{g/ml}$ ) of BPC 157 also increased the expression of vinculin (Figure 3a). The relative band intensities of phospho-paxillin, paxillin and vinculin were shown in Figure 3b.

## DISCUSSION

BPC 157 is a stable 15-amino acid first isolated from human gastric juice, and it is known to exert protective effect on different tissues or organs.<sup>[18]</sup> In addition to the action on various gastrointestinal lesions, the potentially beneficial effects on pancreas, liver injuries, endothelium and heart damage, inflammation, wound and fracture healing are also described.<sup>[19]</sup> BPC 157 has also been reported on promoting muscle injury.<sup>[9]</sup> Our previous

study showed BPC 157 accelerated initial outgrowth of tendon fibroblasts from tendon explant, similar to the very early stage of tendon regeneration.<sup>[17]</sup>

Skeletal muscle healing after injury involves progressive overlapping cellular behaviors, such as proliferation, migration, and differentiation of muscle precursors.<sup>[20]</sup> Skeletal muscle satellite cells are quiescent stem cells which are localized between the plasmalemma and the basement membrane of muscle fiber. Once muscle injury, satellite cells are activated and migrate to the injured site. The cells differentiate to form new myofibers which fuse to each other or fuse to local surviving muscle fibers, contributing to muscle regeneration.<sup>[21,22]</sup>

Cell migration is an important cellular behavior during muscle healing. It can be divided into three distinct stages; protrusion (spreading) in which lamellipodia and filopodia are extended forward over the extracellular matrix; attachment in which the actin cytoskeleton connects to the adhesion sites and interacts with other focal adhesion proteins; and traction in which the cell body moves forward.<sup>[23]</sup> Our study revealed that BPC 157 had a significant effect on promoting skeletal muscle cell spreading, and enhancing cell migration.

Paxillin can interact directly or indirectly with a number of proteins which have been implicated in regulating the cytoskeletal architecture and processes such as spreading and migration. Paxillin is tyrosine phosphorylated by FAK, and linked to Cas via the adapter protein Crk, and Cas plays a role in cell migration through the activation of Rac.<sup>[24-26]</sup> Paxillin also interacts with vinculin during focal adhesion, these two proteins have independent function involved in cell cytoskeletal dynamics.<sup>[27,28]</sup> In the protrusion stage of cell migration, vinculin is localized in the leading edge of the cell and regulate membrane protrusion.<sup>[29]</sup> Following the protrusion stage, vinculin interacts with F-actin, talin and Cas and triggers actin-cytoskeleton modification. The mechanical stress which presented by the linkage between vinculin and F-actin activate other molecules and increase the intensity linkage with vinculin-actin filament and strengthen focal adhesion.<sup>[30]</sup> We have confirmed BPC 157 increased F-actin formation of tendon fibroblasts after BPC 157 treatment. BPC 157 activated the phosphorylation levels of FAK and paxillin and promoted cell migration of tendon fibroblasts.<sup>[17]</sup> In this study, the

protein expressions of paxillin and vinculin were also up-regulated by BPC 157.

Previous study has shown BPC 157 promoted myofiber regeneration in injured muscle in animal model. BPC 157 given in injured site or intraperitoneally after muscle crush injury accelerated post-injury muscle healing.<sup>[9]</sup> Our study implied that the regulation of protein expressions of paxillin and vinculin might be a critical molecular mechanism for BPC 157 induced *in vitro* healing and migration of skeletal muscle cell. Taken these studies together, BPC 157 may accelerate muscle healing by regulating the migration capacity of skeletal muscle cell. However, BPC 157 showed no toxicity and side effects in trials and was effective in low dose.<sup>[31]</sup> It may be a new treatment on muscle injury.

## CONCLUSION

In conclusion, these findings provide novel information about the molecular mechanism of BPC 157 to enhance muscle cell migration. BPC 157 promotes migration and spreading of skeletal muscle cells in association with the up-regulation of expressions of paxillin and vinculin. These findings provide laboratory evidence to support the potential use of BPC 157 on muscle injury.

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# BPC 157 胜肽增加 Paxillin 和 Vinculin 蛋白表現量 以促進骨骼肌細胞移行

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BPC 157 為一穩定的十五胜肽(GEPPPGKPADDAGLV)，最早於人類胃酸中分離出來。目前已知 BPC 157 可促進受傷肌肉組織復原。細胞移行為肌肉癒合過程重要關鍵之一，本研究目的為探討 BPC 157 對於骨骼肌細胞移行之分子機制。利用大鼠腓腸肌分離出骨骼肌細胞，以此細胞處理 BPC 157 後，進行後續研究。細胞移行能力以細胞遷移實驗驗證、細胞擴展以顯微鏡觀察，並以西方墨點法驗證骨骼肌細胞中 paxillin 和 vinculin 兩種蛋白質的表現量。Paxillin 和 vinculin 兩種蛋白質在細胞移行中擔任重要角色。研究結果顯示 BPC 157 促進細胞移行及擴展，且 paxillin 和 vinculin 兩種蛋白質的表現量上升。結果可知 BPC 157 藉由增加 paxillin 和 vinculin 兩種蛋白質的表現量，促進骨骼肌細胞移行及擴展之能力。(台灣復健醫誌 2019；47(1)：21 - 29)

**關鍵詞：**BPC 157 胜肽(BPC 157)、骨骼肌細胞(skeletal muscle)、細胞移行(cell migration)

