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ORIGINAL RESEARCH

Effects of Uridine and Uridine Nucleotides on Proliferation and Migration of L929 Murine Fibroblast Cell Line

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ABSTRACT

The present study aimed to investigate the effects of uridine and the uridine nucleotides uridine-5'-monophosphate (UMP), uridine-5'-diphosphate (UDP) and uridine-5'-triphosphate (UTP) at different concentrations (1, 10 and 100 µM) on cell viability and migration capacity using the L929 murine fibroblast cell line. To assess cytotoxicity and cellular proliferation, the MTT [(3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide)] assay was performed at 24, 48 and 72 hours of incubation, providing a quantitative evaluation of metabolic activity and cell survival. Additionally, the scratch assay was employed and followed up to 96 hours to analyze fibroblast migration, offering insights into the role of these pyrimidines in wound healing and tissue repair. The MTT assay revealed that the highest concentration (100 µM) of UMP or UDP significantly enhanced proliferation of cells at 72 hours while uridine at 10 and 100 µM and UTP at all concentrations tested provided the same effect. In scratch assay UMP or UDP did not cause any significant cell migration while uridine and UTP, at all concentrations, significantly enhanced migration of fibroblast cells at 96 hours. The results demonstrated distinct effects of uridine and its nucleotides on cell viability and migration, with significant benefit in terms of wound healing provided by uridine and UTP, highlighting their potential biological significance and therapeutic implications in regenerative medicine and tissue engineering.

Keywords: Uridine. L929 murine fibroblast cells. MTT. Proliferation. Migration. Wound healing.

Uridin ve Uridin Nükleotidlerinin L929 Fare Fibroblastik Hücrelerinin Proliferasyonu ve Göçü Üzerindeki Etkileri

ÖZET

Bu çalışmanın amacı, üridin ve üridin nükleotidleri üridin-5'-monofosfat (UMP), üridin-5'-difosfat (UDP) ve üridin-5'-trifosfat (UTP)'ın farklı konsantrasyonlarda (1, 10 ve 100 µM) uygulanmasının L929 kemirgen fibroblast hücre kültüründe hücre canlılığı ve göç etme kapasitesine etkilerini incelemektir. Sitotoksisite ve hücresel proliferasyonu değerlendirmek için 24, 48 ve 72 saatlik inkübasyonların sonunda metabolik aktivite ve hücre canlılığı konusunda kantitatif değerlendirme yapılmasını sağlayan MTT [3-(4,5-dimetiltiazol-2-il)-2,5-difeniltetrazolyum bromür] testi uygulandı. Ayrıca bu pirimidin bileşiklerinin yara iyileşmesi ve doku tamiri konusundaki etkilerini incelemek üzere çizik testi yapılarak fibroblast göçü 96 saate kadar takip edildi. MTT testi ile 72 saat inkübasyon sonunda UMP veya UDP'nin en yüksek (100 µM) konsantrasyonda hücre proliferasyonunu artırırken üridin'in 10 ve 100 µM konsantrasyonlarda ve UTP'nin denenen tüm konsantrasyonlarında aynı etkiyi gösterdiği tespit edildi. Çizik testinde UMP veya UDP anlamlı hücre göçüne neden olmazken 96 saat inkübasyon sonrası üridin ve UTP denenen tüm konsantrasyonlarında hücre göçünü anlamlı olarak artırdı. Bu sonuçlar üridin ve üridin nükleotidlerinin hücre proliferasyonu ve göçü üzerine farklı etkileri olduğunu ve yara iyileşmesi bakımından üridin ve UTP'nin anlamlı faydaları olabileceğini göstermekle birlikte rejeneratif tıp ve doku mühendisliği alanlarındaki potansiyel biyolojik önemlerine ve terapötik kullanımlarına işaret etmektedir.

Anahtar Kelimeler: Üridin. L929 kemirgen fibroblast hücreleri. MTT. Proliferasyon. Migrasyon. Yara iyileşmesi.

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Nucleotides are essential biomolecules that are crucial in various biological processes within living organisms. They are the basic building blocks of nucleic acids that store and transmit genetic information. They also participate in intracellular signaling pathways and contribute to enzymatic reactions. Through these diverse functions, nucleotides support cellular metabolism, communication and genetic regulation, making them indispensable for life[1].

Uridine is the major circulating pyrimidine nucleoside in humans, which is also found in

tissues freely or in phosphorylated forms (nucleotides) such as uridine-5'-monophosphate (UMP), uridine-5'-diphosphate (UDP), and uridine-5'-triphosphate (UTP)[2]. Uridine and uridine nucleotides play a crucial role in RNA synthesis, protein and lipid glycosylation, and membrane biosynthesis by serving as vital components of intracellular metabolic pathways and various biosynthetic processes, highlighting their significance in maintaining overall cellular balance and physiological stability[3]. In addition to their physiological roles, several studies reported anti-apoptotic[4], anti-inflammatory[5] and anti-oxidative[6] effects of uridine as well as extracellular matrix (ECM) modulation[7] on exogenous administration. Moreover, uridine has been recently identified as a conserved pro-regenerative factor by cross-species metabolomic analyses[8].

Fibroblasts, the predominant cells of the connective tissue, are essential for maintaining structural integrity and facilitating key physiological processes such as wound healing, tissue regeneration and regulation of inflammatory responses[9]. Fibroblasts actively synthesize and secrete collagen, along with other ECM components, providing structural support and promoting cellular communication within tissues[10]. Additionally, fibroblasts play a dynamic role in modulating immune responses by interacting with immune cells and releasing cytokines[11]. The L929 murine fibroblast cell line serves as a well-established model for in vitro research, offering valuable insights into cytotoxicity assays, wound healing mechanisms and cellular stress response[12].

Previous studies have shown that pyrimidine nucleotides can influence cell cycle progression to induce cellular proliferation and differentiation. For example, UTP was shown to enhance proliferation of adult multipotent neural stem cells derived from adult rodent subventricular zone[13] and stimulate dopaminergic differentiation in human mesencephalic neural stem/precursor cell line[14]. UTP was also associated with increased migration of rat cardiac fibroblasts as a profibrotic action[15]. fibroblast viability and wound healing, a recent study showed that uridine-loaded polycaprolactone (PCL) nanofiber mats enhanced the viability of L929 fibroblast cells in vitro in MTT assay and accelerated wound healing in vivo on rats[16]. Despite this limited information, little is known about the effects of other pyrimidine compounds such as UMP and UDP on cell proliferation and wound healing.

Therefore, the present study aimed to comprehensively investigate, as well as compare, the effects of uridine and uridine nucleotides on viability and migration of cultured L929 murine fibroblast cells. The effects of pyrimidines on viability and proliferation were analyzed by MTT assay and on migration and wound closure were assessed by scratch assay.

Material and Method

Chemicals

The chemicals that were used in this study and the suppliers that they were purchased are as follows: uridine (Cat. No: U3750), UMP (Cat. No: U6375), UDP (Cat. No: 94330), UTP (Cat. No: U6875), sodium dodecyl sulfate (SDS; Cat. No: 11667289001) and *N,N*-dimethylformamide (DMF; Cat. No: 227056) were purchased from Sigma-Aldrich (St. Louis, MO, USA); Dulbecco's Modified Eagle's Medium (DMEM; Cat. No: 30-2002), fetal bovine serum (FBS; Cat. No: 30-2021), L-Glutamine solution (Cat. No: 30-2214) and penicillin-streptomycin solution (Cat. No: 30-2300) were purchased from the American Type Culture Collection (ATCC; Bethesda, MD, USA); and MTT [(3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide)] assay kit (Cat. No: M6494) was purchased from Thermo Fisher Scientific (Waltham, MA, USA).

Cell Culture

L929 murine fibroblast cell line (American Type Culture Collection, LGC Promochem, Rockville, MD, USA) was used throughout the study. They were cultured in a high-glucose DMEM medium (containing 4 mM L-glutamine, 1% penicillin-streptomycin and 10% FBS) at 37°C in a humidified incubator with 5% CO_2. The cells were passaged every two days and experiments were conducted when they reached 80-90% confluency.

MTT Cell Viability Assay

The MTT assay was performed to investigate the effect of uridine and uridine nucleotides on cell viability. L929 murine fibroblast cells were seeded into 96-well plates at a density of $30x10^3$ cells/100 µL and incubated for 24 hours. Uridine, UMP, UDP and UTP were dissolved with the culture medium at different amounts and then administered at 1, 10 and 100 µM concentrations onto cells in the culture. Control group only received the culture medium. Cells were incubated with the culture medium either not containing (control) or containing the pyrimidines for 24, 48 and 72 hours.

On completion of incubation, cells were incubated for an additional 4 hours with the addition of 25 µL of MTT solution (5 mg/ml) to each well to allow for the formation of formazan crystals within the

cell. Formazan was then solubilized by adding 80 µL of a solubilizing solution containing 23% SDS and 45% DMF followed by overnight incubation. Next day, optical density (OD) in each well was detected using a microplate reader (µQuant, Biotek, Winooski, VT, USA) at 570 nm. Cell viability was expressed as percentage change in OD compared to control values.

Scratch Assay

Scratch assay was performed to evaluate the effect of pyrimidines on the migratory ability of L929 cells. The cells were seeded into 6-well plates and cultivated until they reached 100% confluence. A vertical scratch was made on the monolayer cell surface using a P1000 pipette tip. Then 2 ml of the culture medium without (as control) or with 1, 10 and 100 µM uridine, UMP, UDP or UTP was added onto cells and the cells were incubated for 24 hours. Scratch areas were visualized by an inverted light microscope and images were taken at 0, 24, 48, 72 and 96 hours. Images were analyzed using Image J software and percentage of wound closure was calculated. The image taken from the light microscope was uploaded to the ImageJ program and processed. After threshold resetting, the FFT and bandpass filter were selected. FFT Analysis (Fast Fourier Transform) transforms signals from the time domain to the frequency domain. This step can lead to investigating numerous signal characteristics, much more than when inspecting the time domain data. Adjusting the threshold, the most apparent contrast was obtained for the cell and the space (distance). The distance value was obtained in pixels by selecting the wand (tracing) tool. Different time points data normalized to day 0 data (initial day distance).

Wound closure % formula=

$$100 - \left(\frac{end\ time\ points\ pixel\ x\ 100}{initial\ day\ pixel}\right).$$

Statistical Analysis

Statistical analyses were performed using GraphPad Prism software. Data were expressed as mean ± standard error of means (SEM). All experiments were repeated at least three times at separate times (biological replication). In addition, cells were seeded in at least two wells from each condition, and technical replication was performed. Shapiro-Wilk test was used to evaluate whether the data are normally distributed or not. One-Way ANOVA followed by post-hoc Tukey test was used to compare the groups if the data were normally distributed. If not, Kruskal-Wallis followed by post-hoc Dunn's test was applied with Bonferroni's correction. Level of significance was set at $p<0.05$.

Results

Cell Viability

Cell viability was assessed by MTT assay at 24, 48 and 72 hours of incubation and expressed as percentage of proliferation in comparison to control group at each time point (Figure 1). At 24 hours, significantly increased cell viability was observed with uridine at 10 and 100 µM concentrations ($p<0.01$), UMP at 10 µM ($p<0.05$) and 100 µM ($p<0.001$) concentrations, UDP at 10 µM ($p<0.01$) and 100 µM ($p<0.001$) concentrations and with UTP at all concentrations tested ($p<0.01$ for 1 and 10 µM and $p<0.001$ for 100 µM). At 48 hours, significantly increased cell viability was observed with uridine at 10 µM ($p<0.01$) and 100 µM ($p<0.001$) concentrations and UTP at 10 and 100 µM concentrations ($p<0.001$). UMP or UDP had no significant effect on cell viability at 48 hours incubation. At 72 hours, significantly increased cell viability was observed with uridine at 10 µM ($p<0.01$) and 100 µM ($p<0.001$) concentrations, UMP at 100 µM concentration ($p<0.01$), UDP at 100 µM concentration ($p<0.001$) and with UTP at all concentrations tested ($p<0.001$ for 1 and 100 µM and $p<0.01$ for 10 µM).

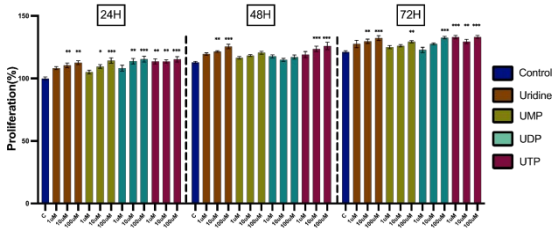

Figure 1:
*Results of MTT assay performed to assess the effect of uridine, UMP, UDP and UTP administered at 1, 10 and 100 µM concentrations on cell viability at 24, 48 and 72 hours of incubation. Data were expressed as mean ± SEM of three independent experiments and presented as % proliferation. *p<0.05, **p<0.01 and p<0.001 compared to control group within each time point.*

Cellular Migration

Cellular migration was assessed by scratch assay at 24, 48, 72 and 96 hours of incubation and expressed as percentage of wound closure compared to control group at each time point (Figure 2). Percentage of wound closure was similar and did not differ significantly in all groups at around 25%, 50% and 70% at 24-, 48- and 72-hours incubation, respectively. At 96 hours however, percentage of

wound closure was significantly greater at all uridine concentrations ($p<0.05$ for 1 and 10 μM and $p<0.01$ for 100 μM) as well as in UTP groups at all concentrations ($p<0.01$) compared to the control group. UMP or UDP had no significant effect on wound closure at any period of incubation. Figure 3 shows a representative image of scratch assay for each group at each time point.

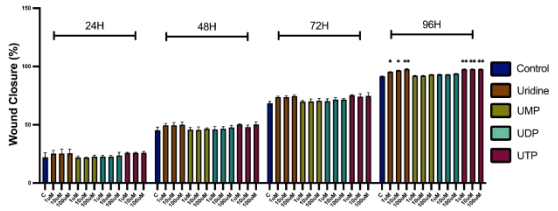

Figure 2:
*Results of scratch assay performed to assess the effect of uridine, UMP, UDP and UTP administered at 1, 10 and 100 μM concentrations at 24, 48, 72 and 96 hours of incubation on cellular migration. Data were expressed as mean ± SEM of three independent experiments and presented as % wound closure. *p<0.05, **p<0.01 and p<0.001 compared to control group within 96 hours.*

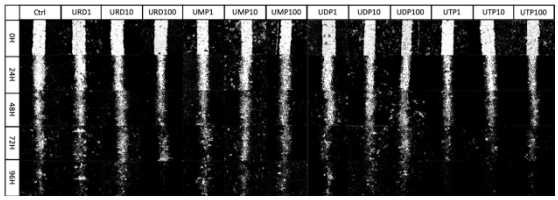

Figure 3:
Representative images of scratch assay containing wound closure effects of uridine, UMP, UDP and UTP administered at 1, 10 and 100 μM concentrations from day 0 to day 4 (96 hours).

Discussion and Conclusion

These data show that exogenous administration of the pyrimidine nucleoside uridine and its nucleotides UMP, UDP and UTP all enhances cell viability in cultured L929 murine fibroblast cells while only uridine or UTP significantly increases cellular migration, suggesting their beneficial effect on wound closure. To the best of our knowledge, our study is the first to investigate these pyrimidine compounds on viability and migration of fibroblast cells.

Uridine is the major circulating pyrimidine nucleoside in humans which is also found in breast milk and tissues freely or as a constituent of pyrimidine nucleotides[2]. Uridine and uridine nucleotides play a crucial role in RNA synthesis, protein and lipid glycosylation and membrane biosynthesis by serving as vital components of intracellular metabolic pathways and various biosynthetic processes[3]. Exogenous administration of uridine has been shown to confer benefit in experimental models of hypoxic-ischemic[4] or hyperoxic[6] brain damage and peripheral nerve injury[17] through mechanisms involving inhibition or alleviation of apoptosis[4,18], inflammation[5], oxidative stress[6,18] and modulation of epigenetic mechanisms[4,19] or the ECM composition[7].

Cell proliferation and migration are essential components of wound healing which also involves hemostasis and maturation[20]. Along with thrombocytes, macrophages are critical to the hemostasis stage which are involved in fibroblast proliferation and migration. Fibroblasts are key to this proliferative stage since they actively participate in collagen production[21]. Additionally, fibroblasts provide structural support and promote cellular communication within tissues[10] by also playing a dynamic role in modulating immune responses by interacting with immune cells and releasing cytokines[11]. Hence, fibroblasts represent a valuable tool for studies of wound healing[9]. The L929 murine fibroblast cell line has been widely recognized as a good candidate for such studies due to its reproducibility and responsiveness to various stimuli which offers valuable insights into cytotoxicity (proliferation) assays and wound closure (cellular migration) studies[12].

Not much is known about the effect of pyrimidines on cell proliferation or wound healing. Available data showed that uridine-loaded polycaprolactone (PCL) nanofiber mats enhanced the viability of L929 fibroblast cells in vitro in MTT assay and accelerated wound healing in vivo on rats[16]. UTP was shown to enhance proliferation of adult multipotent neural stem cells[13] and stimulate dopaminergic differentiation in human mesencephalic neural stem/precursor cell[14]. UTP was also reported to increase migration of rat cardiac fibroblasts as a profibrotic response[15]. Besides, the involvement or effects of UMP or UDP in these processes have not yet been evaluated. Therefore, the present study investigated the effects of uridine and uridine nucleotides on proliferation and migration of cultured L929 murine fibroblast cells to gain further insight into the potential contribution of pyrimidines in wound healing.

The results of the present study showed that uridine and uridine nucleotides all enhanced cell proliferation especially at high doses after 72 hours of incubation. The effect of uridine or UTP was

stronger compared to UMP or UDP in terms of fibroblast proliferation. The data also showed that uridine or UTP, but not UMP or UDP, significantly enhanced cellular migration, ensuring a greater recovery and wound closure in the scratch assay.

The reason why uridine or UTP was effective in stimulating wound closure, but UMP or UDP was not, must be further studied. One possible explanation might involve receptor activation by the pyrimidines. While no receptor has been described for uridine or UMP to date, the uridine nucleotides UDP and UTP have been shown to exhibit their effects by stimulating a number of G-protein coupled P2Y receptors. UDP activates P2Y6 and P2Y14 receptors and UTP activates P2Y2 and P2Y4 receptors[22]. Stimulation of P2Y2, P2Y4 and P2Y6 receptors causes phospholipase C activation which is followed by intracellular calcium accumulation while stimulation of P2Y14 receptors inhibits adenylate cyclase to reduce cAMP levels[22]. The expression of any of these receptors on L929 murine fibroblast cells has not been documented, therefore it would only be speculative to discuss the receptor mediation of the effects. Moreover, no receptor has yet been described for uridine while it is involved in several physiological functions and is beneficial in different disease models in vivo. Therefore, investigation of the mechanism of action of pyrimidines in proliferation and migration of fibroblasts remains as a limitation of this study.

In conclusion, the present study investigated the effects of uridine and uridine nucleotides on proliferation and migration of L929 murine fibroblast cells and showed, for the first time, that all tested pyrimidines enhanced fibroblast proliferation, but migration was only enhanced by uridine or UTP. These data enhance our knowledge of the effects of pyrimidines on fibroblast behavior and provide new insights into wound healing and tissue regeneration.

Ethics Committee Approval Information:
Not applicable.
Researcher Contribution Statement:
Idea and design: G.G., D.Y.E.; Data collection and processing: E.E., D.Y.E., S.C., Analysis and interpretation of data: D.Y.E., E.E., Writing of significant parts of the article: G.G., D.Y.E., E.E., H.B.O.
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Conflict of Interest Statement:
The authors of the article have no conflict of interest declarations.

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