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Bidirectional Crosstalk Between Bladder Cancer Cells and Normal Fibroblasts Drives Phenotypic Reprogramming and Modulates Chemosensitivity

Jinhui Gao[1*], Cindy Xinyu Ji[1,2], John Hines[3], Eleanor Stride[4], Richard T. Bryan[5], Jennifer L. Rohn[1*]

1 Division of Medicine, University College London, London, UK
2 Cancer Research UK Manchester Institute, University of Manchester, Manchester, UK
3 Westmoreland Street University College London Hospital, London, UK
4 Institute of Biomedical Engineering, Department of Engineering Science, University of Oxford, Oxford, UK
5 Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham, UK

*Corresponding author email: andy.gao@ucl.ac.uk; j.rohn@ucl.ac.uk

Bladder cancer is one of the most common malignancies worldwide and is marked by high recurrence rates, highlighting the urgent need to better understand the tumour microenvironment (TME). While the role of cancer-associated fibroblasts (CAF) in cancer progression and therapy resistance is well established, the contribution of normal fibroblasts (NF) remains underexplored. Here we dissect bidirectional interactions between bladder cancer cells and NF using indirect (conditioned media) and direct co-culture systems. Fibroblast-conditioned media (FCM) reduced proliferation in RT112 and T24 cells while accelerating cell migration. Immunofluorescence revealed a cadherin remodelling with increased N-cadherin and reduced E-cadherin after FCM exposure. On the stromal side, NF acquired CAF-like features within 48 h, with αSMA and FAP increases evidenced by imaging in conditioned media and confirmed by flow cytometry in direct co-culture. In addition, direct co-culture reduced mitomycin C (MMC) efficacy in a fibroblast-ratio dependent manner in both cancer cell lines. It suggests that fibroblast composition in the TME may influence individual variability in treatment response. These findings highlight a significant role for NF in modulating bladder cancer behaviour and therapeutic resistance, supporting the need to consider fibroblast-cancer interactions in developing more effective treatment strategies.

Key words: Bladder Cancer, Normal fibroblast, Cancer associated fibroblast, Tumour microenvironment, Mitomycin C

Introduction

Overview of Bladder Cancer

Bladder cancer remains one of the most prevalent malignancies worldwide, ranking among the top ten cancers of incidence and mortality (1). It is categorised into two main types based on the extent of invasion into the bladder wall: non-muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC). NMIBC, including stages Ta, T1, and carcinoma in situ (Tis), accounts for approximately 70–80% of newly diagnosed cases (2). NMIBC is characterised by high recurrence rates, ranging from 50% to 80% depending on grade and stage, and an estimated 10–20% of cases eventually progress to MIBC, which carries a much poorer prognosis (3).
The current standard of care for NMIBC includes transurethral resection of bladder tumour (TURBT), often followed by intravesical instillation of chemotherapeutic agents such as mitomycin C (MMC) or immunotherapy using Bacillus Calmette–Guérin (BCG). Although BCG immunotherapy has demonstrated efficacy in reducing recurrence and progression, its utility is frequently hindered by side effects, poor patient tolerance, and the development of resistance or immune escape mechanisms (4). Chemotherapeutic agents like MMC suffer from limited tissue penetration and variable patient responses, particularly in cases where tumour microenvironmental factors contribute to drug resistance (5). Radical cystectomy remains the definitive treatment for high-risk or BCG-unresponsive NMIBC, but it carries substantial morbidity and can significantly impact quality of life (6). These challenges underscore the need to better understand the underlying factors driving treatment failure and disease progression.

Tumour Microenvironment of Bladder Cancer

A critical factor influencing both treatment efficacy and cancer progression is the tumour microenvironment (TME), which remains insufficiently characterised in bladder cancer (7). The dynamic interactions between cancer cells and their surrounding stromal components

are key determinants of therapeutic response, chemoresistance, and immune evasion. Cancer-associated fibroblasts (CAFs) represent a central component of the reactive stroma. CAFs exerts their influence through both direct and indirect mechanisms, including the secretion of cytokines, engagement in cell-cell interactions, and extensive remodelling of the extracellular matrix (ECM) (8). Through excessive ECM deposition, CAFs contribute to the architectural integrity of the tumour and modulate biomechanical signalling by forming a fibrotic capsule that encases tumour cells (9). Additionally, CAFs interact with infiltrating immune cells within the TME, thereby shaping the immune landscape and facilitating cancer progression (10).

The Role of Normal Fibroblast in Bladder Cancer

CAFs exhibit significant plasticity and can originate from multiple cell types, including NF, stellate cells, bone marrow-derived mesenchymal stem cells (MSCs), adipocytes, and others (11). Yet NF, the likely precursors of many CAF, are comparatively under-characterised in bladder cancer. NF are particularly important due to their presence in the lamina propria, a thin layer of connective tissue composed of ECM, fibroblasts, endothelial cells, smooth muscle cells, and immune cells (12). This is crucial because bladder cancer originates in the urothelium (NMIBC) and must pass through the lamina propria before eventually invading the detrusor muscle layer, progressing to a more aggressive form (MIBC) as part of the metastatic process (13).

While extensive research has elucidated the role of CAFs in tumourigenesis and metastasis (8), relatively little is known about the functional contributions of NF. Two features of tumour progression particularly implicate NF signals: (i) phenotypic plasticity of cancer cells, including EMT-like cadherin remodelling that enhances migration/invasion; and (ii) CAF-like activation of fibroblasts, typically marked by αSMA and FAP upregulation. Both processes have been described across cancers but remain incompletely mapped in bladder cancer and rarely examined bidirectionally. Studies in other tumour types, such as lung (14), colorectal (15), and pancreatic cancers (Prieto-García et al. 2021), have demonstrated that NF can actively modulate cancer behaviour. Furthermore, cancer cells co-cultured with NF have been shown to exhibit altered phenotypes, including enhanced cell migration and invasive potential, often mediated by ECM remodelling (16). We hypothesise that bladder cancer cells and normal fibroblasts (NFs) influence each other bidirectionally: NFs reprogramme cancer cells toward migratory, therapy-resistant states, while cancer cells reprogramme NFs into CAF-like populations that further reduce chemotherapy efficacy.

Here, we elucidated the role of NF in bladder cancer progression using a co-culture model. Specifically, we investigated the bidirectional interactions between NF and bladder cancer cells on their proliferation and migration. We also assessed whether co-culture conditions induce a phenotypic shift in cancer as well as NF toward a CAF-like state and evaluated the response of these co-cultures to mitomycin C (MMC) treatment.

Results

Indirect Co-Culture reveals Bidirectional Growth Inhibition on Bladder Cancer and NF Cell Proliferation

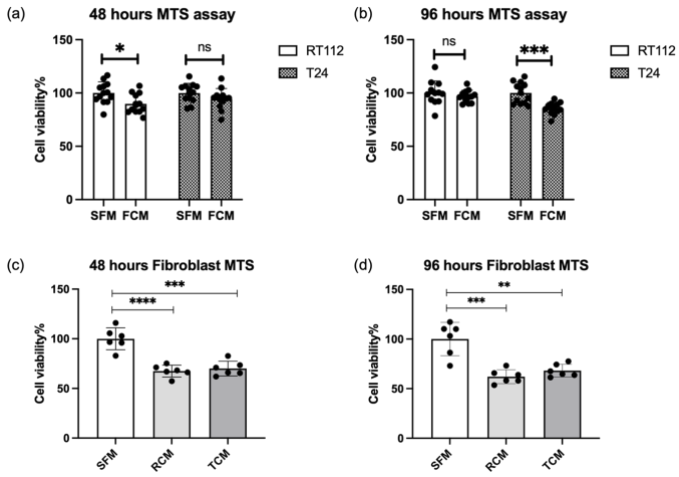

Figure 1: (a, b) Bar charts showing the proliferation of RT112 (low-grade) and T24 (high-grade) bladder cancer cell lines after 48 and 96 hours of treatment with FCM compared to serum-free DMEM (SFM). (c, d) Bar charts showing the proliferation of NF at 48 and 96 hours following exposure to bladder cancer cell-conditioned media derived from RT112 (RCM) and T24 (TCM) compared to SFM.

To explore the bidirectional effects between cancer cells and NF, we first assessed how FCM influenced cancer cell proliferation, and subsequently assessed how cancer cell-conditioned media affected NF's proliferation. To investigate the effect of FCM on cancer cell proliferation, MTS assays were conducted on RT112 and T24 bladder cancer cell lines. FCM treatment significantly reduced the proliferation of RT112 cells in 48 hours, while no significant change was observed in T24 cells. However, a significant reduction in T24 cell proliferation emerged in 96 hours (Figure 1a, b).

In a complementary experiment, the impact of cancer cell-conditioned media on NF proliferation was assessed. NF were treated with RT112-conditioned media (RCM) or T24-conditioned media (TCM), and proliferation was measured using the MTS assay. Both RCM and TCM significantly suppressed NF's proliferation at 48 and 96 hours. RCM reduced proliferation by 67.5% at 48 hours and 62.2% at 96 hours, while TCM led to reductions of 70.0% and 68.2%, respectively, relative to untreated controls (Figure 1c, d).

Indirect Co-Culture with NF Promotes Bladder Cancer Cell Migration and Induce a Cadherin shift

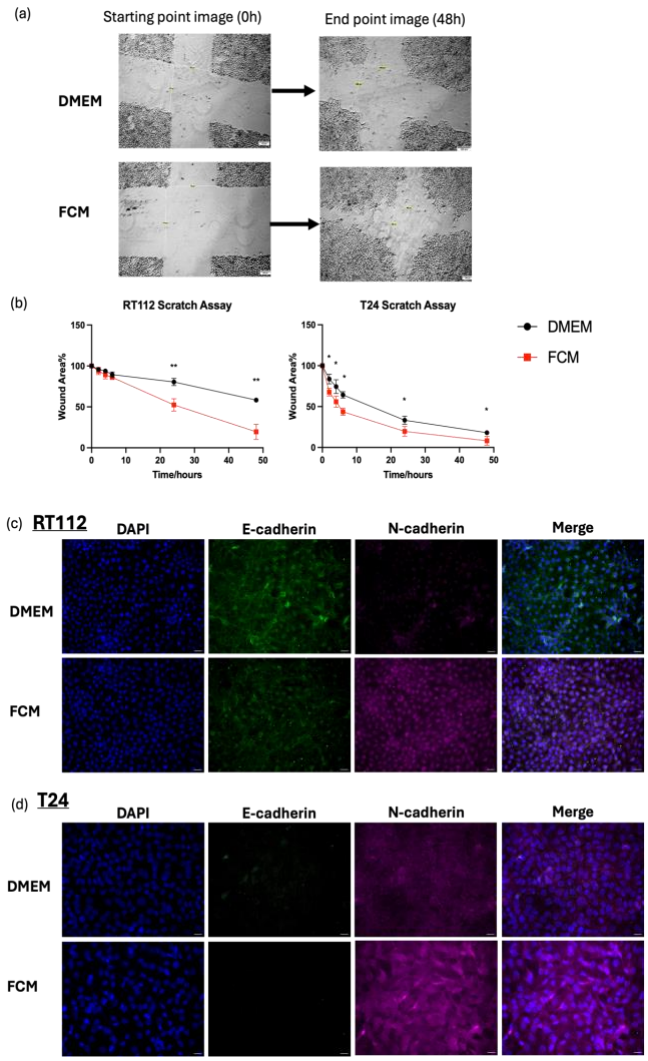

Figure 2: (a) Representative wound healing assay images of RT112 and T24 monolayers at the starting point (0 h) and endpoint (48 h) cultured in control medium (DMEM) or normal-fibroblast conditioned medium (FCM). Scale bars: 100µm. (b) Quantification of wound closure over time expressed as residual wound area (%) for RT112 (left) and T24 (right). FCM consistently increases the rate of wound closure compared with DMEM. Data are mean ± SD; n = 3; (c–d) Immunofluorescence for E-cadherin (green) and N-cadherin (magenta) with DAPI (blue) in RT112 (c) and T24 (d) after 48 h in DMEM or FCM. Immunofluorescence images taken at 40× magnification. Scale bars: 10µm.

In both RT112 and T24 cultures, wound area closure progressed over time in control medium (DMEM) as well as in FCM; however, exposure to FCM significantly accelerated wound closure compared with controls (Figure 2a, b). The effect was most pronounced in RT112 cells, which consistently exhibited enhanced migration at both 24 and 48 hours, resulting in a significant difference between the FCM and DMEM curves. T24 cells also responded to FCM with increased migratory activity, but the effect was more evident at early time points, with statistically significant differences detectable within the first 2 hours of culture. To further determine whether enhanced migration was associated with the cadherin shift, we examined cadherin expression by immunofluorescence after 48 hours in FCM or control medium. In both RT112 and T24, FCM exposure induced a marked reduction in E-cadherin and upregulation of N-cadherin (Figure 2c,d). This cadherin switch is a canonical molecular feature of epithelial-to-mesenchymal transition (17) and is consistent with the functional increase in migration observed in the wound healing assay.

Induction of CAF-Associated Markers in NF Following Indirect and Direct Co-Culture with Bladder Cancer Cells

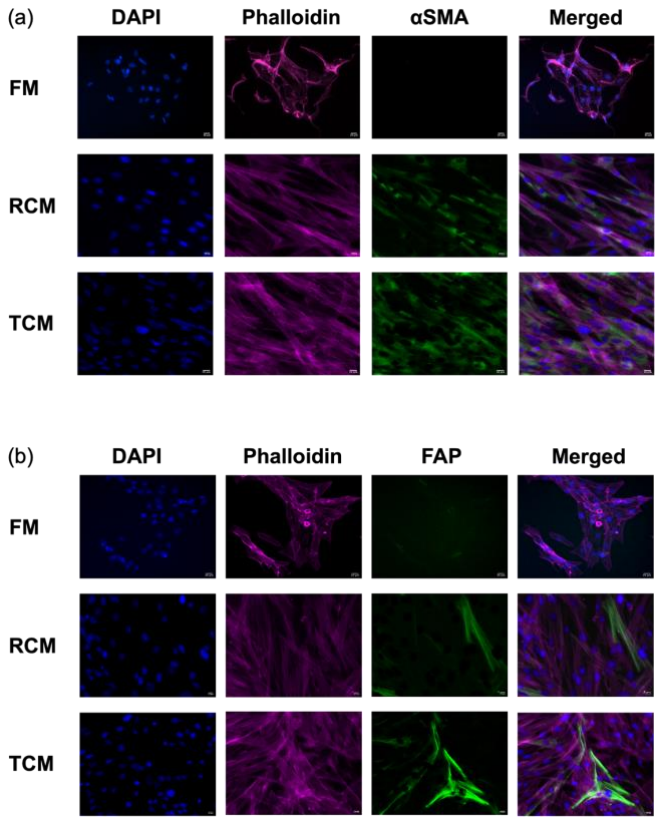

Figure 3: Detection of αSMA (a) and FAP (b) expression in NF after 48 hours of indirect co-culture with cancer-conditioned media. Immunofluorescence images taken at 20× magnification, showing positive green fluorescence indicating the presence of αSMA and FAP markers in NF; n=3; scale bars: 10µm.

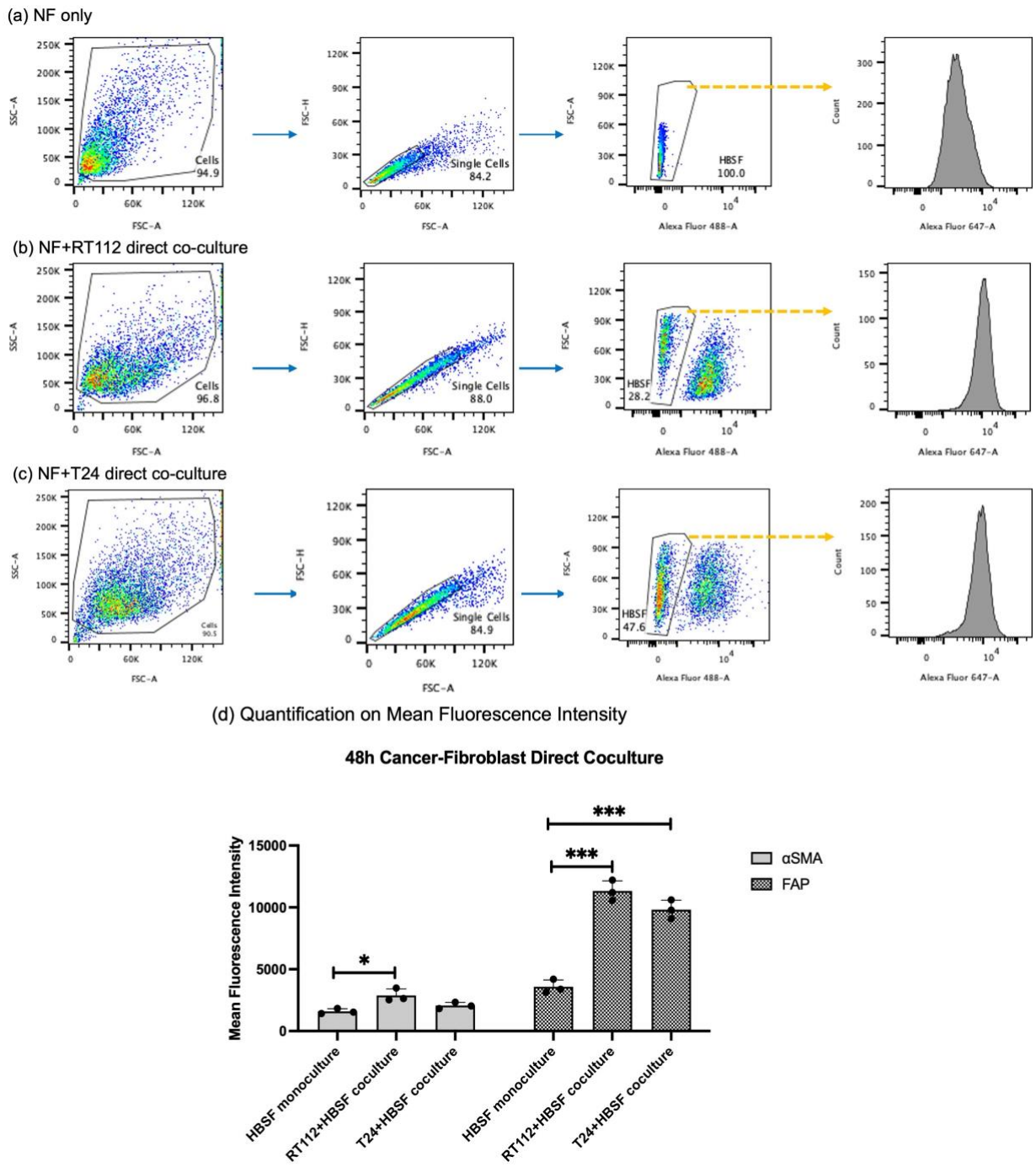

Figure 4: (a–c) Flow-cytometry workflow and representative plots for (a) NF alone, (b) NF co-cultured with RT112, and (c) NF co-cultured with T24 for 48 h. Gates show total cells (FSC-A vs SSC-A), singlets (FSC-H vs FSC-A), and the HBSF population identified by Alexa Fluor 488 negative (pre-labelled cancer with CellTracker Green). The frequency of gated HBSF within each condition is indicated. Right-hand histograms display activation-marker staining in gated HBSF (αSMA/FAP; Alexa Fluor 647 channel).
(d) Quantification of mean fluorescence intensity (MFI) for αSMA and FAP in HBSF monoculture versus direct co-culture with RT112 or T24 (48 h). Both co-cultures significantly increased fibroblast activation marker expression, with the strongest induction observed in T24–HBSF. Bars show mean ± SD from n = 3.

To investigate whether cancer cells influence fibroblast activation, we examined the effect of cancer cell-conditioned media on NF in an indirect co-culture system. Specifically, we assessed the induction of cancer-associated fibroblast (CAF)-like features by evaluating the expression of CAF markers, αSMA and FAP, after 48 hours of treatment. Immunofluorescence (IF) staining was used to visualise protein expression in NF treated with FM, RCM, or TCM. As shown in Figure 3a and 3b, images are arranged by condition in rows (FM, RCM, TCM) and by staining in columns: DAPI (nuclei, blue), Phalloidin (F-actin, red), αSMA or FAP (green), and a merged overlay. In both RCM- and TCM-treated NF. αSMA and FAP staining were visibly increased, particularly in the TCM group, indicating enhanced activation toward a CAF-like phenotype.

Next, NF were cultured alone or in direct co-culture with RT112 or T24 for 48 h, and expression of αSMA and FAP was quantified by flow cytometry. In monoculture, fibroblasts expressed low basal levels of αSMA (1590.7 ± 210.4 MFI) and FAP (3575.0 ± 552.2 MFI). Co-culture with RT112 significantly increased fibroblast activation, with αSMA rising to 2880.0 ± 522.7 and FAP more than tripling to 11,325.0 ± 823.0 (Figure 4d). T24 co-culture also enhanced fibroblast activation, with αSMA reaching 2063.7 ± 257.6 and FAP induced to 9823.3 ± 755.5. These results demonstrate that bladder cancer cells promote fibroblast activation through upregulation of αSMA and FAP. The results revealed that both RT112 and T24 significantly upregulated αSMA and FAP relative to fibroblast monoculture. Moreover, RT112 co-culture induced significantly higher αSMA expression than T24, whereas FAP induction was comparably strong in both RT112 and T24 groups.

MMC showed Less Effectiveness in Cancer-NF Direct Co-Culture with a Higher Fibroblast Ratio

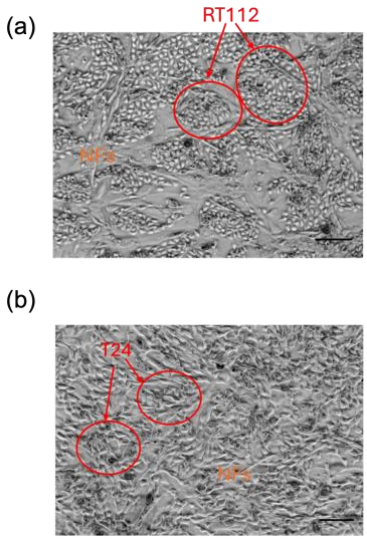

Figure 5: Brightfield images of direct coculture, 1:1 cell seeding ratio coculture HBSF with RT112 (a) and T24 (b), images taken at 10× magnification, Scale bar: 100µm

To further explore the bidirectional interactions between cancer cells and NF, we investigated whether direct co-culture alters the behavior of both cell types. Brightfield microscopy images captured after 48 hours of 1:1 direct co-culture of RT112/NF and T24/NF demonstrated distinct morphological differences between fibroblasts and cancer cells (Figure 5). In the RT112/NF co-culture, NF retained their typical elongated, spindle-shaped morphology and were observed forming discrete clusters with clear intercellular gaps. By contrast, the T24/NF co-culture exhibited a more compact cellular arrangement, with fewer visible gaps and a denser distribution of cancer cells interspersed with NF.
To understand how the presence of NF in the bladder cancer tumour microenvironment (TME) influences the efficacy of the chemotherapy drug MMC, we conducted direct co-culture experiments using RT112 and T24 bladder cancer cells co-cultured with NF at 1:1 and 1:2 ratios. Our results demonstrate that fibroblasts significantly reduce the effectiveness of MMC in both cancer cell lines. Specifically, when cancer cells were co-cultured with fibroblasts at a 1:2 ratio, the normalized drug efficacy decreased to 83.6% in RT112 and 63.5% in T24. Notably, the inhibitory effect was more pronounced in the T24 cell line, where even at a 1:1 co-culture ratio, MMC efficacy was significantly reduced to 79.1% (Figure 6).

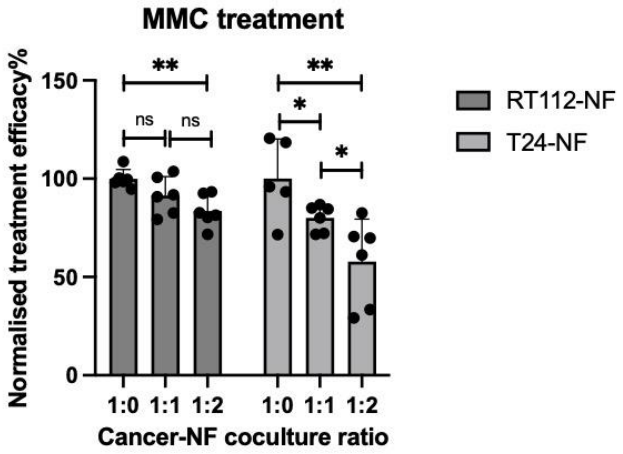

Figure 6: The normalised treatment efficacy (%) of mitomycin C (MMC) in the presence of normal fibroblasts (NFs), compared to cancer cells alone. Bladder cancer cell lines RT112 and T24 were co-cultured with NFs at 1:1 and 1:2 ratios.

Discussion

Our findings demonstrate a bidirectional interplay between fibroblasts and bladder cancer cells in the coculture system. First, NF-conditioned media suppress tumour cell proliferation while enhancing migration, accompanied by an EMT-like cadherin shift. Second, cancer-conditioned media drive fibroblast activation toward CAF-like states, evidenced by increased αSMA and FAP. Third, increasing fibroblast abundance decrease MMC efficacy in direct co-culture. Together, these findings support a bidirectional model in which tumour–stromal interactions promote tumour cell migration and, in parallel, reprogramme fibroblasts into drug-modulating CAF-like states.
The wound healing assay demonstrated that cancer cell migration was significantly enhanced in indirect co-culture with NF, while the MTS proliferation assay revealed a reduction in cancer cell proliferation under the same conditions. These results support the "go or grow" hypothesis, which suggests that cells either migrate or proliferate, but not both simultaneously (18). Our findings indicate that NF may drive cancer cells toward a migratory phenotype.

We also observed that NF in direct co-culture with cancer cells, especially with RT112, showed significant upregulation of αSMA and FAP, indicating a shift towards CAF-like characteristics. This pattern suggests that grade- or lineage-specific tumour may differentially engage αSMA or FAP-linked CAF programmes. Beyond this, fibroblast activation has important immune implications. Recent studies showed CAF can suppress NK cell or T cell infiltration and activity within the TME (19,20), our study provides a rational to investigate whether NF-derived CAF-like population also shape immune surveillance in bladder cancer.

Another critical finding is the role of NF in modulating chemotherapy sensitivity. MMC is a widely used chemotherapy agent for bladder cancer, but its efficacy is limited by poor drug penetration into tumour tissues. In our study, we found that the presence of NF, particularly at higher fibroblast-to-cancer cell ratios, significantly reduced the efficacy of MMC. These findings suggest that both the proportion of fibroblasts and their activation state may be a useful predictor of intravesical chemotherapy response and a therapeutic target. It should be noted, however, that the fibroblast-to-cancer cell ratios tested here are simplified, in vivo stromal composition of bladder tumour is heterogeneous and varies across patients and disease stage. Further work using patient-derived cancer organoid or spatial transcriptomic data will be essential to establish physiologically relevant fibroblast burdens and validate their predictive value for treatment response.

In summary, NF suppress cancer-cell proliferation while promoting migration, and cancer cells reciprocally educate fibroblasts toward CAF-like states marked by αSMA and FAP upregulation. These effects exhibit cell line-specific dynamics rather than a uniform dependence on grade. Importantly, increasing fibroblast abundance reduces MMC efficacy in direct co-culture, underscoring the role of tumour–stroma interaction in shaping drug response. Together, these findings suggest that targeting fibroblast-mediated programmes alongside intravesical chemotherapy may enhance therapeutic outcomes in bladder cancer.

Materials and Methods

Cell culture

Bladder cancer cell lines RT112 (low-grade), T24 (high-grade), and human bladder stromal fibroblasts (HBSF; referred to as normal fibroblasts, NF) were sourced from ATCC and ScienCell Research Laboratory. Cancer cells were cultured in T25 flasks using Dulbecco's Modified Eagle Medium (DMEM; Gibco) supplemented with 10% fetal bovine serum (FBS; Fisher Scientific) and 1% Penicillin/Streptomycin (Gibco). NF were cultured in Fibroblast Medium (FM; ScienCell #2301), consisting of basal medium supplemented with 2% FBS, 1% fibroblast growth supplement, and 1% antibiotic solution.

Cells were maintained at 37°C in a 5% CO_2 incubator. Once cells reached ~80% confluence, medium was removed, cells were washed with phosphate-buffered saline (PBS; Gibco), and detached using Accutase (Merck). After neutralisation with complete medium, the cell suspension was centrifuged at 300 × g for 6 minutes, resuspended in fresh medium, and transferred to new flasks for expansion.

Conditioned Medium Preparation

Serum-free DMEM was used to eliminate FBS-associated variability. RT112, T24, and NF were seeded in T150 flasks respectively. After 24 hours, media were replaced with serum-free DMEM containing 1% Penicillin/Streptomycin. After 48 hours of incubation, conditioned media RCM, TCM, and FCM were harvested, centrifuged to remove debris, filtered through 0.2 μm filters (Fisher Scientific), and stored at 4°C for subsequent experiments.

MTS Cell Proliferation Assay

a. Bidirectional Effects of NF and Cancer Cells Using Conditioned Medium

To assess the effect of FCM on cancer cells, 3000 RT112 or T24 cells/well were seeded in 96-well plates (6 replicates/condition). After 24 hours, cells were washed with PBS and treated with serum-free DMEM or FCM. After 48 or 96 hours of incubation, MTS reagent (Promega) was added and incubated for 2 hours. Absorbance was read at 490 nm using a Tecan plate reader. To assess the reverse interaction, NF were treated with RCM, TCM, or serum-free DMEM, following the same approach.

b. Effect of MMC on Bladder Cancer Cells in Direct Co-culture

RT112 or T24 cells were co-cultured with NF at 1:0, 1:1, and 1:2 ratios (total 6000 cells/well) in 96-well plates. After 24 hours, cells were treated with mitomycin C (MMC; 20 μM) for 1 hour, washed with PBS, and incubated in fresh medium for 72 hours before performing MTS assay as described above.

Scratch Assay – Cell Migration

RT112 (2.5×10^5) and T24 (2.0×10^5) cells were seeded in 24-well plates and allowed to reach confluence over 48 hours. A linear scratch was made using a 1 mL pipette tip, followed by media replacement. Images were captured at 0, 2, 4, 6, 24, and 48 hours using a Leica microscope. Wound area was measured using LAS X software and normalised to time zero:

$$\widehat{A}(t) = \frac{A(t)}{A(0)} \times 100\%$$

Immunofluorescence of indirect coculture

NF (3×10^4 cells/well) were seeded on μ-slide 8-well chamber slides (ibidi) and incubated for 24 hours. Media were replaced with DMEM, RCM, or TCM for 48 hours. On the cancer side, RT112 or T24 Cells (3×10^4 cells/well) were seeded on μ-slide 8-well chamber slides (ibidi) and incubated for 24 hours. Media were replaced with DMEM, FCM for 48 hours. Cells then fixed in 4% formaldehyde (FA), permeabilised with 0.2% Triton X-100, and blocked with 5% normal goat serum and 1% BSA. For NF, primary antibodies against fibroblast activation protein (FAP) and α-smooth muscle actin (αSMA) (Cell Signaling Technology) were applied at 1:100 overnight at 4°C. After washing, secondary antibody (anti-rabbit Alexa Fluor 488; Invitrogen) was applied for 45 minutes. F-actin was stained using Alexa Fluor 555 Phalloidin (Thermo Fisher Scientific), and nuclei were counterstained with DAPI. For Cancer, E-Cadherin (Mouse-Invitrogen) (10ug/ml) and N-Cadherin (Rabbit-Invitrogen) (1ug/ml) were applied overnight at 4°C. After washing, secondary antibody (anti-mouse Alexa Fluor 488; Invitrogen and anti-rabbit Alexa Fluor 555) was applied for 45 minutes, and nuclei were counterstained with

DAPI. Images were acquired using a Leica-Mica or widefield microscope.

Intracellular Staining for CAF-associated Markers via Flow Cytometry

αSMA and FAP Expression (direct Co-culture)
NF were cultured in T75 flasks with RT112 or T24 cancer cells in the ratio of 1:1, detached with Accutase, and fixed with 4% FA. After permeabilisation with 0.2% Triton X-100 and blocking with 5% normal goat serum, cells were stained with αSMA or FAP primary antibodies (1:100) for 45 minutes. Secondary antibody (anti-rabbit Alexa Fluor 488) was applied for 30 minutes. After washing, cells were resuspended in 1% BSA and analysed using a BD LSRFortessa flow cytometer. Data were processed using FlowJo software.

Statistical Analysis

All data were analysed using unpaired two-tailed t-tests with a 95% confidence interval. A p-value ≤ 0.05 was considered statistically significant. *: $p \leq 0.05$; **: $p \leq 0.01$; ***: $p \leq 0.001$; ****: $p \leq 0.0001$. Data are presented as mean ± standard error of the mean. GraphPad Prism (version 10.3.0) was used for statistical testing and graphing.

Declaration

Declarations of interest: none

CRediT authorship contribution statement

JG: Conceptualization; Methodology; Investigation; Funding acquisition; Supervision; Writing original draft; Review & editing; CXJ: Investigation; Methodology, Writing original draft; Review & editing; JH: Review & editing; ES: Funding acquisition; Supervision; Review & editing. RTB: Funding acquisition; Supervision; Review & editing. JLR: Funding acquisition; Supervision; Review & editing.

Funding:

We thank the Rosetrees Trust (CF-2022-2_124) and Action Bladder Cancer UK IOPP Grant 2025 for funding the project.

References:

1. Richters A, Aben KKH, Kiemeney LALM. The global burden of urinary bladder cancer: an update. World J Urol. 2020 Aug;38(8):1895–904.

2. Cox E, Saramago P, Kelly J, Porta N, Hall E, Tan WS, et al. Effects of Bladder Cancer on UK Healthcare Costs and Patient Health-Related Quality of Life: Evidence From the BOXIT Trial. Clin Genitourin Cancer. 2020 Aug;18(4):e418–42.

3. Grabe-Heyne K, Henne C, Mariappan P, Geiges G, Pöhlmann J, Pollock RF. Intermediate and high-risk non-muscle-invasive bladder cancer: an overview of epidemiology, burden, and unmet needs. Front Oncol. 2023 June 2;13:1170124.

4. Askeland EJ, Newton MR, O'Donnell MA, Luo Y. Bladder Cancer Immunotherapy: BCG and Beyond. Adv Urol. 2012;2012:1–13.

5. Wang C, Li A, Yang S, Qiao R, Zhu X, Zhang J. CXCL5 promotes mitomycin C resistance in non-muscle invasive bladder cancer by activating EMT and NF-κB pathway. Biochem Biophys Res Commun. 2018 Apr;498(4):862–8.

6. Claps F, Pavan N, Ongaro L, Tierno D, Grassi G, Trombetta C, et al. BCG-Unresponsive Non-Muscle-Invasive Bladder Cancer: Current Treatment Landscape and Novel Emerging Molecular Targets. Int J Mol Sci. 2023 Aug 9;24(16):12596.

7. The Tumor Microenvironment of Bladder Cancer. In: Advances in Experimental Medicine and Biology [Internet]. Cham: Springer International Publishing; 2020 [cited 2025 May 1]. p. 275–90. Available from: https://link.springer.com/10.1007/978-3-030-59038-3_17

8. Huang L, Xie Q, Deng J, Wei WF. The role of cancer-associated fibroblasts in bladder cancer progression. Heliyon. 2023 Sept;9(9):e19802.

9. Barbazan J, Pérez-González C, Gómez-González M, Dedenon M, Richon S, Latorre E, et al. Cancer-associated fibroblasts actively compress cancer cells and modulate mechanotransduction. Nat Commun. 2023 Nov 1;14(1):6966.

10. Mao X, Xu J, Wang W, Liang C, Hua J, Liu J, et al. Crosstalk between cancer-associated fibroblasts and immune cells in the tumor microenvironment: new findings and future perspectives. Mol Cancer. 2021 Oct 11;20(1):131.

11. Xu Y, Li W, Lin S, Liu B, Wu P, Li L. Fibroblast diversity and plasticity in the tumor microenvironment: roles in immunity and relevant therapies. Cell Commun Signal. 2023 Sept 18;21(1):234.

12. Stead RH, Tomioka M, Pezzati P, Marshall J, Croitoru K, Perdue M, et al. Interaction of the Mucosal Immune and Peripheral Nervous Systems. In: Psychoneuroimmunology [Internet]. Elsevier; 1991 [cited 2025 Apr 10]. p. 177–207. Available from: https://linkinghub.elsevier.com/retrieve/pii/B9780120437801500105

13. Lokeshwar SD, Lopez M, Sarcan S, Aguilar K, Morera DS, Shaheen DM, et al. Molecular Oncology of Bladder Cancer from Inception to Modern Perspective. Cancers. 2022 May 24;14(11):2578.

14. Greenwell JC, Torres-Gonzalez E, Ritzenthaler JD, Roman J. Fibroblast-derived conditioned media promotes lung cancer progression. Am J Med Sci. 2023 Feb;365(2):189–97.

15. Koh B, Jeon H, Kim D, Kang D, Kim K. Effect of fibroblast co-culture on the proliferation, viability and drug response of colon cancer cells. Oncol Lett [Internet]. 2018 Dec 14 [cited 2025 Apr 10]; Available from: http://www.spandidos-publications.com/10.3892/ol.2018.9836

16. Liu C, Mak M. Fibroblast-mediated uncaging of cancer cells and dynamic evolution of the physical microenvironment. Sci Rep. 2022 Jan 17;12(1):791.

17. Loh CY, Chai J, Tang T, Wong W, Sethi G, Shanmugam M, et al. The E-Cadherin and N-Cadherin Switch in Epithelial-to-Mesenchymal Transition: Signaling, Therapeutic Implications, and Challenges. Cells. 2019 Sept 20;8(10):1118.

18. Crossley RM, Painter KJ, Lorenzi T, Maini PK, Baker RE. Phenotypic switching mechanisms determine the structure of cell migration into extracellular matrix under the 'go-or-grow' hypothesis. Math Biosci. 2024 Aug;374:109240.

19. Jenkins L, Jungwirth U, Avgustinova A, Iravani M, Mills A, Haider S, et al. Cancer-Associated Fibroblasts Suppress CD8+ T-cell Infiltration and Confer Resistance to Immune-Checkpoint Blockade. Cancer Res. 2022 Aug 16;82(16):2904–17.

20. Ben-Shmuel A, Gruper Y, Halperin C, Levi-Galibov O, Rosenberg-Fogler H, Barki D, et al. Cancer-Associated Fibroblasts Serve as Decoys to Suppress NK Cell Anticancer Cytotoxicity in Breast Cancer. Cancer Discov. 2025 June 3;15(6):1247–69.