Development and mechanistic evaluation of an extended-release LPAR2 agonist as a radiation medical countermeasure

PhD thesis

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1. Introduction

Acute radiation syndrome (ARS) is a life-threatening condition resulting from exposure to high doses of ionizing radiation. The severity of ARS depends on radiation dose and the tissues affected, with injury to the hematopoietic and gastrointestinal systems representing the primary determinants of morbidity and mortality. While several medical countermeasures have been approved for treatment of the hematopoietic subsyndrome of ARS (H-ARS), effective therapies targeting the gastrointestinal subsyndrome (GI-ARS) remain lacking. GI-ARS results from radiation-induced loss of rapidly proliferating intestinal crypt stem cells, leading to failure of epithelial regeneration, disruption of intestinal barrier integrity, and systemic complications including sepsis and multi-organ failure. Because large-scale radiation exposure events would require rapidly deployable therapeutic strategies, the development of countermeasures capable of mitigating gastrointestinal radiation injury represents an important objective in radiation medicine and public health preparedness.

Cellular responses to radiation injury are governed by the balance between apoptotic signaling pathways and pro-survival mechanisms that promote tissue recovery. Among the signaling pathways implicated in radiation response, the extracellular signal-regulated kinase (ERK) and phosphoinositide-3-kinase/Akt pathways play central roles in regulating cell survival, proliferation, and stress adaptation. Pharmacologic strategies capable of activating these pathways may therefore enhance cellular resilience and support regeneration following radiation exposure.

Lysophosphatidic acid (LPA) is a bioactive phospholipid that regulates diverse cellular processes through activation of a family of G protein–coupled receptors (LPAR1–6). Activation of lysophosphatidic acid receptor subtype 2 (LPAR2) has been shown to promote intestinal epithelial survival and mitigate radiation-induced apoptosis through engagement of downstream ERK and Akt signaling pathways. Previous work from our laboratory has focused on the development of non-lipid LPA analogs capable of selectively activating LPAR2 as potential radiation countermeasures. Early lipid-based agonists such as octadecenyl thiophosphate (OTP) demonstrated radioprotective activity, while subsequent medicinal chemistry efforts produced small-molecule

agonists with improved potency and pharmacologic properties. Radioprotectin-1 (RP-1) represents a potent third-generation LPAR2-specific agonist that activates pro-survival signaling pathways and enhances cellular recovery following radiation exposure.

In addition to receptor-mediated signaling pathways, stress-responsive genes play important roles in regulating cellular responses to radiation injury. The immediate early response gene IEX-1 (IER3) is rapidly induced following cellular stress and has been implicated in the regulation of mitochondrial function, oxidative stress, and apoptosis. IEX-1 has also been shown to interact with ERK signaling pathways, suggesting that it may influence survival responses following radiation exposure. However, the role of IEX-1 in determining tissue radiosensitivity *in vivo* remains incompletely understood.

2. Objectives

The overall aim of this work was to investigate signaling pathways that influence cellular responses to ionizing radiation and to evaluate pharmacologic strategies for mitigating radiation-induced injury. This thesis examined mechanisms regulating survival signaling in gastrointestinal and hematopoietic radiation injury and assessed the translational potential of LPAR activation as a radiation countermeasure. The specific objectives of this study were:

- **2.1** To optimize the pharmacokinetic profile of the LPAR2 agonist RP-1 through development of an extended-release microemulsion (ME) formulation.
- **2.2** To evaluate whether extended-release RP-1 administration improves survival outcomes and preserves intestinal integrity in a murine model of GI-ARS.
- **2.3** To characterize the impact of LPAR2 activation on pro-survival signaling pathways following irradiation.
- **2.4** To determine the contribution of IEX-1 to hematopoietic and gastrointestinal radiosensitivity and to explore the relationship to stress-response signaling pathways.

3. Methods

3.1 Animal models of ARS

Specific pathogen-free C57BL/6J mice were used for pharmacologic studies, while B6;129X1-Ier^{3tm1Raku}/J (IEX-1 knockout [KO]) mice were used to investigate the effects of IEX-1 deficiency on radiation response.

Murine models of both H- and GI-ARS were employed. Hematopoietic injury was induced by 9 Gy total body irradiation (TBI), while gastrointestinal injury was modeled using 16 Gy partial body irradiation with approximately 5% bone marrow shielding (PBI-BM5). Irradiation was performed using a ^{137}Cs source irradiator at a dose rate of ≤1 Gy/min, with radiation doses selected based on previously established lethal dose-response parameters for each model. Survival following irradiation was monitored for 21 days for PBI-BM5 GI-ARS model or 30 days for TBI H-ARS model, and animals exhibiting severe clinical symptoms were humanely euthanized according to predefined criteria.

3.2 Pharmacologic studies and RP-1 formulation

Radiation mitigation studies initiated at 24 h post-irradiation were conducted using RP-1. To improve the pharmacokinetic (PK) profile of the compound, an extended-release water-in-oil-in-water (W/O/W) ME formulation was developed. This formulation contained RP-1 distributed between an external aqueous (AQ) phase and an internal aqueous reservoir encapsulated within an oil layer, enabling both immediate and sustained drug release. In GI-ARS experiments, RP-1 ME formulation was administered by subcutaneous injection beginning 24 h post-irradiation, with a second dose administered at 72 h. Survival outcomes and intestinal tissue responses were evaluated for radiomitigative efficacy.

3.3 Pharmacokinetic studies

PK studies were performed in both mice and rhesus macaque non-human primates (NHP) to evaluate systemic exposure to RP-1. Following administration of RP-1 formulations, plasma was collected at multiple time points.

Plasma concentrations of RP-1 were quantified using liquid chromatography–tandem mass spectrometry. Plasma samples were spiked with an internal standard and subjected to liquid–liquid extraction using water-saturated butanol. Chromatographic separation was performed using reverse-phase liquid chromatography coupled to a triple quadrupole mass spectrometer operating in multiple reaction monitoring mode. Quantification was based on calibration curves generated using RP-1 standards prepared in pooled blank plasma.
PK parameters including plasma half-life, clearance, and mean plasma residence time were calculated using non-compartmental analysis in Phoenix WinNonlin 8.4.0. These studies were used to compare the PK properties of AQ and ME RP-1 formulations and to assess formulation-driven improvements in systemic drug exposure.

3.4 Histological analysis of intestinal injury

To evaluate gastrointestinal radiation injury, small intestinal tissues were collected from mice treated with vehicle or RP-1 on day 5 following 16 Gy PBI-BM5. Tissue samples were fixed in buffered formalin, embedded in paraffin, and sectioned for histological analysis. Hematoxylin and eosin (H&E) staining was used to assess intestinal morphology and crypt integrity. Immunohistochemical staining of Ki67 was also performed to assess intestinal epithelial proliferation and regeneration. Crypt survival and regenerative capacity were quantified by counting intact and regenerating crypts in intestinal cross-sections.

3.5 Cellular models and signaling assays

Mouse embryonic fibroblasts (MEF) isolated from LPAR1/2 double KO mice stably transfected with human LPA2 receptor (LPA2 MEF) or empty vector (EV MEF) were used to investigate the effects of LPAR stimulation on radiation-induced, pro-survival signaling pathways. All experiments were performed using mycoplasma-free cultures.
MEF were serum-deprived and treated with either LPA or RP-1, then exposed to 15 Gy irradiation. Phosphorylation of ERK1/2 and Akt was quantified using phospho-antibody cell-based ELISA to evaluate signaling kinetics up to 16 h following irradiation. Caspase 3/7 activity assays were also performed using the same treatment paradigm to assess

the effects of LPAR activation on radiation-induced apoptosis using the Promega Caspase-Glo® 3/7 Assay System.

To examine intestinal epithelial growth responses, jejunal and ileal crypts were isolated from wild-type (WT) and IEX-1 KO mice and cultured as three-dimensional enteroids in Matrigel extracellular matrix for 9 days. Enteroids were monitored for growth and differentiation over time by measuring two-dimensional area in ImageJ v1.54 and counting budding villus-like projections, respectively.

ERK signaling in 5 Gy irradiated enteroids was analyzed by immunoblot to assess differences in signaling dynamics between genotypes following radiation exposure. Total protein was separated by 12% SDS-PAGE, transferred to nitrocellulose membranes, and probed for phosphorylated ERK1/2. Blots were stripped and re-probed for total ERK1/2, and densitometric analysis was conducted in Bio-Rad Image Lab 5.2.1 software. Phosphorylated ERK was normalized to total ERK, and data were presented as fold change relative to non-irradiated WT control samples.

3.6 Gene expression analysis

IEX-1 expression was analyzed in mouse whole blood, intestinal mucosa, and enteroid cultures. Total RNA was extracted using the Qiagen RNeasy Protect Animal Blood Kit, RNeasy Lipid Tissue Mini Kit, and RNeasy Micro Kit, respectively. RNA was reverse transcribed using the Thermo Scientific™ RevertAid Reverse Transcriptase Kit. Quantitative real-time PCR (RT-qPCR) was performed using gene-specific primers to measure expression of IEX-1 and related signaling components. Relative expression levels were calculated using the comparative Ct ($\Delta\Delta$Ct) method with normalization to endogenous *Gapdh* or *Rplp0* housekeeping genes, and fold changes in expression were reported relative to untreated non-irradiated controls.

3.7 Statistical analyses

All experimental data are presented as mean ± standard error of the mean (SEM). Survival curves were analyzed using Kaplan–Meier methodology with Mantel-Cox log-rank testing for statistical significance. For comparisons between two independent groups,

unpaired two-tailed t-test was used. For experiments involving more than two groups or multiple time points, one-way or two-way analysis of variance (ANOVA) with Tukey's or Šídák's post hoc testing was used. Statistical analyses were performed using GraphPad Prism v10.4.1, and differences were considered significant at $p < 0.05$.

4. Results

4.1 Pharmacokinetic optimization of RP-1

RP-1 is a selective LPAR2 agonist capable of activating pro-survival signaling pathways following radiation exposure. However, the AQ formulation used in earlier studies exhibited rapid plasma clearance and relatively short systemic exposure, necessitating multiple doses to achieve therapeutic efficacy. To improve the PK properties of RP-1 and enhance its potential applicability as a radiation countermeasure, an extended-release W/O/W ME formulation was developed.

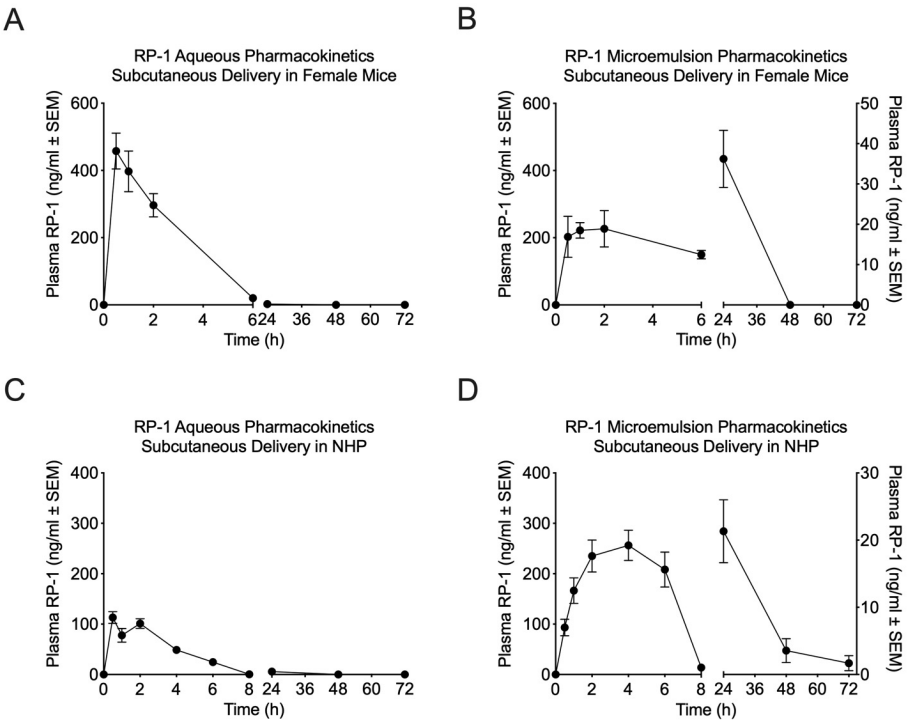

Figure 1. RP-1 ME exhibits an extended-release PK profile in mice and NHP

PK studies were conducted to compare systemic exposure following AQ and ME formulations. Plasma concentrations of RP-1 were quantified using LC-MS/MS in both mice (**Figure 1A-B**) and NHP (**Figure 1C-D**). In both mice and NHP, the ME formulation produced a markedly prolonged exposure profile compared with the AQ formulation, characterized by significant increases in plasma half-life and mean residence time and significant reduction in plasma clearance. These results demonstrate that ME formulation-based optimization significantly improves the PK profile of RP-1 and supports its use in simplified dosing regimens for radiation countermeasure deployment.

4.2 RP-1 mitigates gastrointestinal radiation injury

The radiomitigative efficacy of RP-1 ME was evaluated using a murine model of GI-ARS with PBI-BM5. This model produces severe intestinal injury while preserving a small fraction of bone marrow to permit assessment of survival outcomes. Treatment with RP-1 ME was initiated 24 h following irradiation, consistent with a radiomitigation paradigm. Animals receiving RP-1 demonstrated a significant improvement in survival compared with vehicle-treated controls (**Figure 2**). The extended-release formulation enabled effective mitigation using a simplified dosing schedule consisting of two subcutaneous injections administered at 24 h and 72 h after irradiation. These findings indicate that pharmacologic activation of LPAR signaling significantly improves survival following severe gastrointestinal radiation injury.

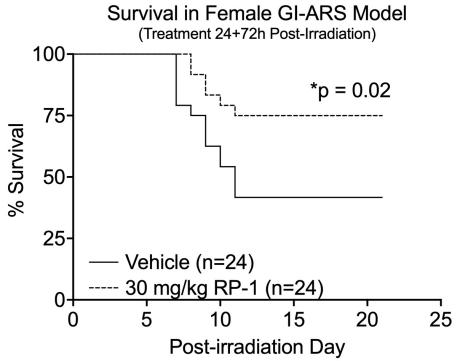

Figure 2. RP-1 ME formulation mitigates GI-ARS.

4.3 RP-1 augments intestinal crypt regeneration

To evaluate the effects of RP-1 treatment on intestinal injury and recovery, histological analyses were performed on small intestinal sections collected following irradiation. H&E staining revealed extensive disruption of the intestinal crypt-villus architecture in irradiated animals. Counting surviving crypts in H&E-stained sections revealed a significant increase in the number of crypts in animals treated with RP-1 compared with vehicle-treated controls (**Figure 3A**). To assess epithelial regenerative activity, sections were additionally stained for Ki67 using immunohistochemistry. Ki67-positive staining identified actively regenerating crypts undergoing proliferative recovery following radiation injury. RP-1-treated animals exhibited increased numbers of Ki67-positive regenerating crypts compared with controls, indicating enhanced epithelial proliferation during the recovery phase (**Figure 3B**). Because intestinal crypts contain the stem and progenitor cells responsible for intestinal epithelial renewal, these findings demonstrate that activation of LPAR2 signaling promotes both crypt survival and regenerative proliferation following radiation exposure.

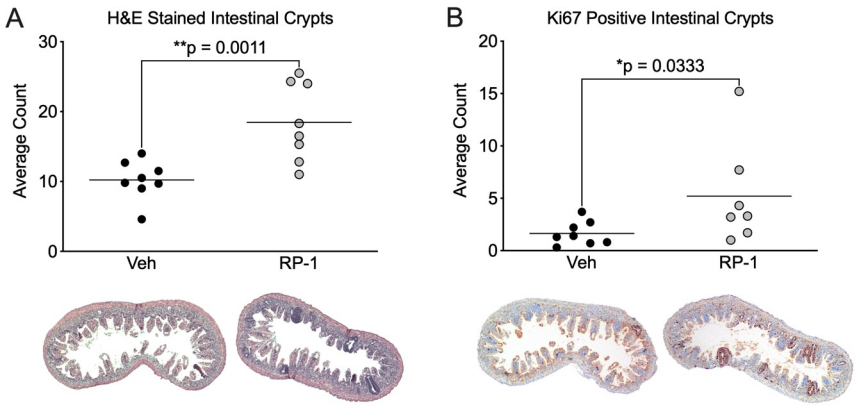

Figure 3. RP-1 ME preserves intestinal crypt architecture and regeneration.

4.4 LPAR activation induces prolonged pro-survival signaling and reduces apoptosis

Activation of LPAR signaling is known to stimulate intracellular pathways that promote survival following cellular stress. To characterize the signaling response associated with LPAR activation, phosphorylation kinetics of ERK and Akt were evaluated in irradiated and non-irradiated EV vs LPA2 MEF following treatment with LPA or RP-1.

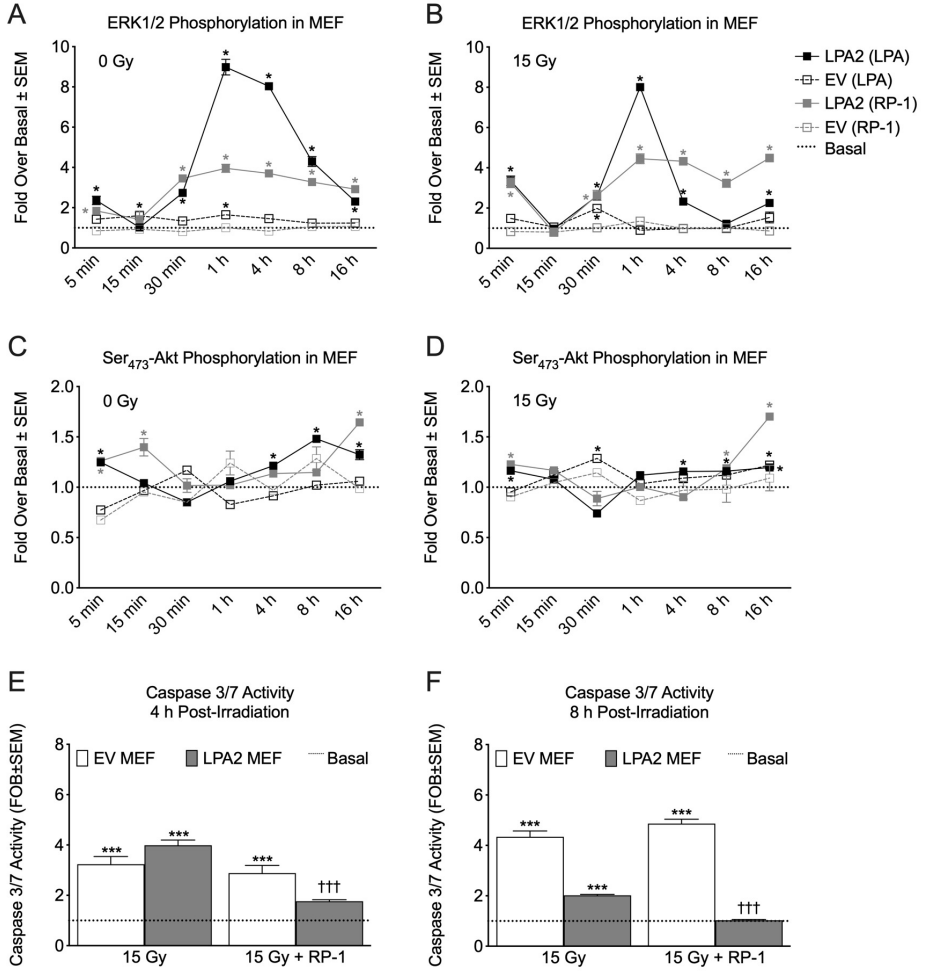

Figure 4. LPAR activation induces pro-survival signaling and reduces apoptosis.

Regardless of irradiation, both LPA and RP-1 treatment resulted in increased phosphorylation of ERK (**Figure 4A-B**) and Akt (**Figure 4C-D**) relative to untreated controls. Notably, both LPA and RP-1 stimulation produced sustained ERK phosphorylation that persisted for up to 16 h following irradiation; however, LPA-induced ERK phosphorylation peaked earlier and declined more rapidly over time. Akt activation was less robust overall but was still significantly elevated 16 h after irradiation upon LPA or RP-1 stimulation. Little to no ERK or Akt phosphorylation was noted in EV MEF, underscoring the necessity of LPAR activation in the pro-survival response.

To determine whether activation of these pro-survival pathways influenced apoptotic responses following irradiation, caspase-3/7 activity was also measured. RP-1 treatment significantly reduced caspase activation compared with irradiated control cells, indicating decreased apoptosis following LPAR stimulation. This effect only occurred in the LPA2 MEF and not the EV MEF. Together, these findings demonstrate that LPAR activation promotes sustained pro-survival signaling while simultaneously suppressing apoptosis following radiation exposure.

4.5 LPAR stimulation induces IEX-1 expression

Expression of IEX-1 was evaluated in WT mouse whole blood and intestinal mucosa as well as in intestinal enteroid cultures. Quantitative gene expression analysis demonstrated that IEX-1 expression was markedly enriched in intestinal mucosal tissue and enteroids compared with whole blood (**Figure 5A**), suggesting a potential role for IEX-1 in intestinal epithelial regenerative capacity under conditions of stress. To investigate whether IEX-1 expression is regulated by LPAR signaling, expression levels were measured following stimulation with LPA and/or OTP and subsequent irradiation at 9 Gy TBI, 16 Gy PBI-BM5, or 5 Gy for, whole blood (**Figure 5B**), intestinal mucosa (**Figure 5C**), and enteroid cultrues (**Figure 5D**) respectively. LPAR activation induced IEX-1 expression *in vivo* in whole blood—beyond that of irradiation alone—and intestinal mucosa, as well as in intestinal enteroid cultures. These results demonstrate that IEX-1 is expressed in radiation-sensitive hematopoietic and intestinal epithelial tissues and can be induced

further by activation of LPAR, supporting further investigation of its contribution to radiosensitivity.

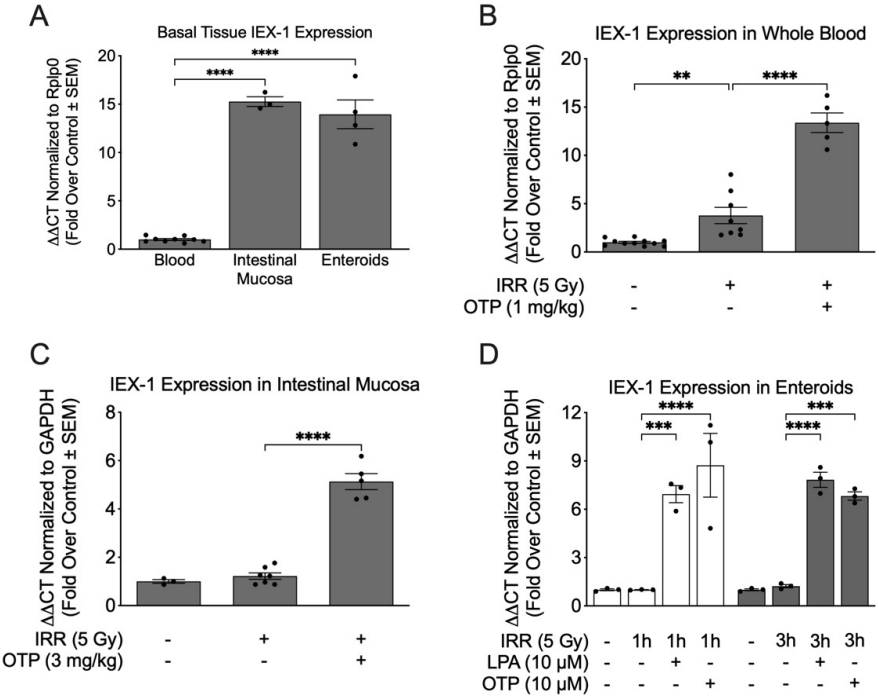

Figure 5. LPAR stimulation induces IEX-1 expression.

4.6 IEX-1 deficiency exacerbates radiation injury

To determine whether IEX-1 influences radiosensitivity, survival outcomes were evaluated in WT and IEX-1 KO mice following radiation exposure. Mice lacking IEX-1 exhibited ~30% reduced survival compared with WT controls following 9 Gy TBI, indicating increased susceptibility to hematopoietic radiation injury (**Figure 6A**). Similarly, in a model of GI-ARS using 16 Gy PBI-BM5, IEX-1 KO mice also demonstrated ~30% decreased survival compared with WT animals (**Figure 6B**). These findings indicate that loss of IEX-1 increases sensitivity to radiation-induced injury in both hematopoietic and gastrointestinal systems and suggest that IEX-1 contributes to protective cellular responses following irradiation.

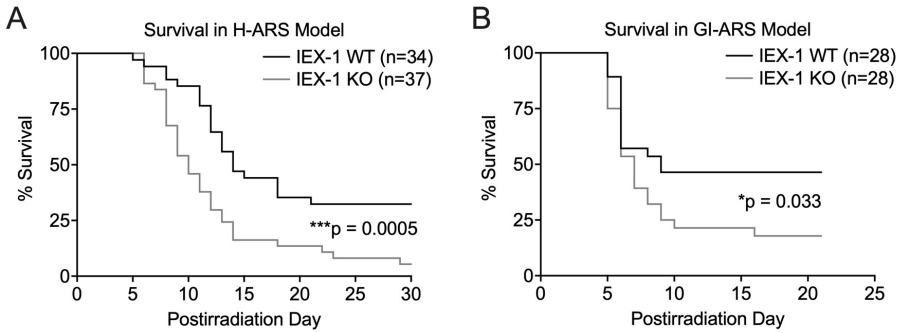

Figure 6. IEX-1 deficiency exacerbates radiation injury.

4.7 Loss of IEX-1 delays enteroid growth and alters ERK signaling

To investigate cellular mechanisms underlying the increased radiosensitivity observed in IEX-1-deficient animals, intestinal enteroids derived from WT and IEX-1 KO mice were examined over a period of 9 days (**Figure 7A**). IEX-1 KO enteroids exhibited delayed growth (**Figure 7B**) and impaired differentiation (**Figure 7C**) compared with WT enteroids over the first 7 days in culture, indicating that IEX-1 may facilitate early intestinal epithelial regeneration in response to stress. Consistent with these observations, histological analysis of intestinal tissue revealed no significant differences in baseline crypt numbers between WT and IEX-1 KO mice, suggesting that the observed phenotype does not result from developmental differences in intestinal crypt density (**Figure 7D**). Immunoblot analysis revealed altered ERK phosphorylation kinetics in IEX-1 KO enteroids in response to radiation. While basal ERK phosphorylation levels were elevated in IEX-1 KO enteroids, early ERK activation following irradiation was reduced relative to WT controls (**Figure 7E**). These findings suggest that IEX-1 plays a role in regulating the temporal dynamics of ERK signaling during cellular stress responses and may influence intestinal epithelial survival and regenerative capacity following radiation exposure.

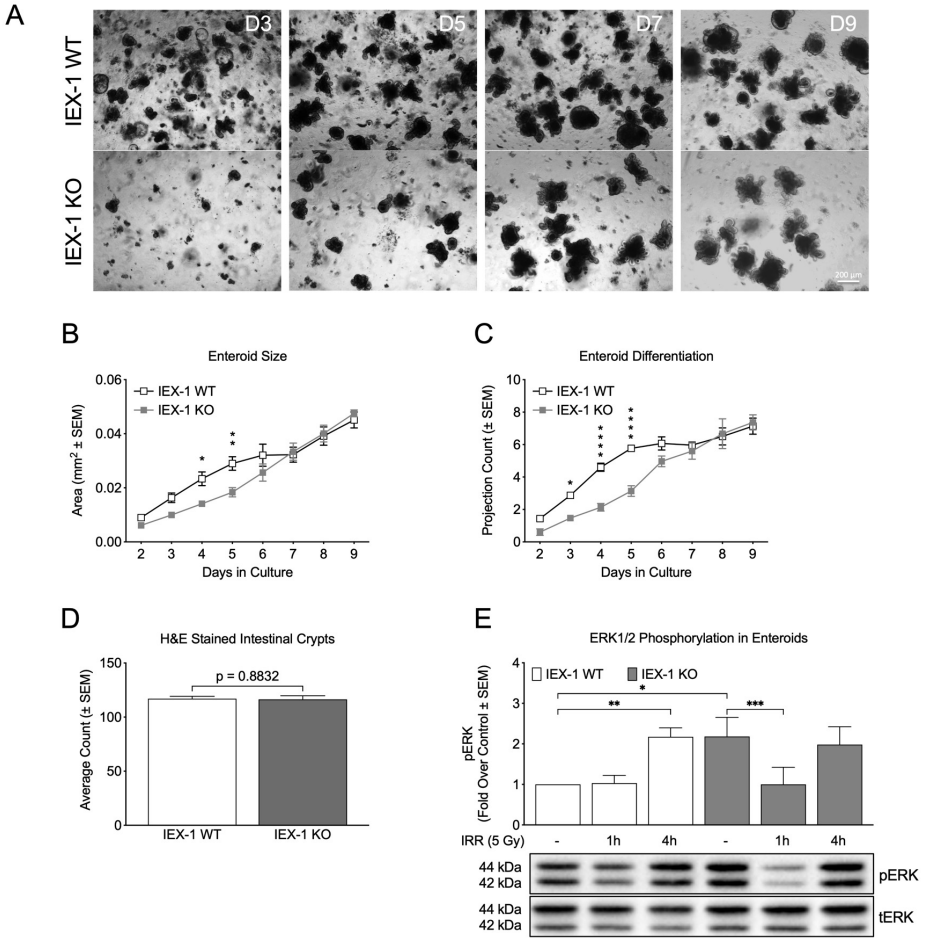

Figure 7. Loss of IEX-1 delays enteroid growth and alters ERK signaling.

5. Conclusions

This work investigated signaling pathways that regulate cellular responses to ionizing radiation and explored strategies for mitigating radiation-induced injury. Using complementary pharmacologic and genetic approaches, the studies presented here examined the role of LPAR signaling and IEX-1 in determining survival outcomes following radiation exposure. The principal conclusions are as follows:

- **Activation of LPAR signaling mitigates GI-ARS.** Treatment with the selective LPAR2 agonist RP-1 improved survival and preserved intestinal crypt architecture in a murine GI-ARS model when administered beginning 24 h post-irradiation.
- **Pharmacokinetic optimization improves the translational feasibility of RP-1.** A multilayered W/O/W ME formulation extended the plasma residence time of RP-1 in both mice and NHP and enabled effective radiation mitigation with a simplified two-dose regimen in a murine GI-ARS model.
- **LPAR activation promotes sustained pro-survival signaling following irradiation.** Stimulation with LPA or RP-1 resulted in prolonged ERK and Akt phosphorylation and reduced caspase-mediated apoptosis *in vitro* in MEF.
- **IEX-1 is a determinant of tissue radiosensitivity.** IEX-1 KO mice exhibited reduced survival in models of both H- and GI-ARS, indicating that IEX-1 contributes to radiation injury response in multiple tissue compartments.
- **IEX-1 influences intestinal epithelial growth dynamics and ERK signaling responses.** Enteroids derived from IEX-1 KO mice displayed delayed growth, impaired differentiation, and altered ERK phosphorylation kinetics following irradiation, and IEX-1 expression was inducible following LPAR stimulation, implying that IEX-1 participates in stress-responsive signaling networks that regulate cellular responses to radiation-induced damage.

Collectively, these findings highlight the importance of survival signaling pathways in determining tissue responses to radiation exposure. The results support continued investigation of LPAR-targeted therapeutics and identify IEX-1 as a regulator of radiosensitivity that may contribute to future strategies for mitigating radiation injury.

6. Bibliography of the candidate's publications

Related to the thesis (**Total IF: 6.088**):

1. **Norman DD**, Shin Y, Balázs L, Benyo Z, Lee SC, Tigyi GJ. Loss of the lysophosphatidic acid-induced immediate early gene IEX-1 exacerbates acute radiation syndrome. Radiat Res. 2026. Submitted under review. (**IF: 2.7**)
2. **Norman DD**, Lee SC, Shin Y, Ibrahim MM, Jablonski MM, Wang Y, Balázs L, Davies EW, Benyo Z, Tigyi GJ. Development of an Extended-release Formulation of Radioprotectin-1 for Mitigation of Gastrointestinal Acute Radiation Syndrome. Radiat Res. 2026. (**IF: 2.7**)
3. Kuo B, Szabo E, Lee SC, Balogh A, **Norman D**, Inoue A, Ono Y, Aoki J, Tigyi G. The LPA(2) receptor agonist Radioprotectin-1 spares Lgr5-positive intestinal stem cells from radiation injury in murine enteroids. Cell Signal. 2018;51:23-33. (**IF: 3.388**)

Not related to the thesis (**Total IF: 181.772**):

1. Rai P, Clark CJ, Kardam V, Womack CB, Thammathong J, **Norman DD**, Tigyi GJ, Bicker K, Weissmiller AM, Dubey KD, Banerjee S. Structure-Based Discovery of MolPort-137: A Novel Autotaxin Inhibitor That Improves Paclitaxel Efficacy. Int J Mol Sci. 2025;26(2). (**IF: 4.9**)
2. Dacheux MA, **Norman DD**, Shin Y, Tigyi GJ, Lee SC. Deleting autotaxin in LysM+ myeloid cells impairs innate tumor immunity in models of metastatic melanoma. iScience. 2024;27(10):110971. (**IF: 4.1**)
3. Hutka B, Varallyay A, Laszlo SB, Toth AS, Scheich B, Paku S, Voros I, Pos Z, Varga ZV, **Norman DD**, Balogh A, Benyo Z, Tigyi G, Gyires K, Zadori ZS. A dual role of lysophosphatidic acid type 2 receptor (LPAR2) in nonsteroidal anti-inflammatory drug-induced mouse enteropathy. Acta Pharmacol Sin. 2024;45(2):339-53. (**IF: 8.4**)

4. Kim TY, Kim A, Aryal YP, Sung S, Pokharel E, Neupane S, Choi SY, Ha JH, Jung JK, Yamamoto H, An CH, Suh JY, Sohn WJ, Lee Y, Jang IH, **Norman DD**, Tigyi GJ, An SY, Kim JY. Functional modulation of lysophosphatidic acid type 2 G-protein coupled receptor facilitates alveolar bone formation. J Cell Physiol. 2024;239(1):112-23. (**IF: 4.0**)
5. Rai P, Clark CJ, Womack CB, Dearing C, Thammathong J, **Norman DD**, Tigyi GJ, Sen S, Bicker K, Weissmiller AM, Banerjee S. Novel Autotaxin Inhibitor ATX-1d Significantly Enhances Potency of Paclitaxel-An In Silico and In Vitro Study. Molecules. 2024;29(18). (**IF: 4.6**)
6. Dacheux MA, **Norman DD**, Tigyi GJ, Lee SC. Emerging roles of lysophosphatidic acid receptor subtype 5 (LPAR5) in inflammatory diseases and cancer. Pharmacol Ther. 2023;245:108414. (**IF: 12.0**)
7. Heo SC, Keum BR, Seo EJ, Yoon J, Jeong S, Tigyi GJ, **Norman D**, Jang IH, Kim HJ. Lysophosphatidic acid induces proliferation and osteogenic differentiation of human dental pulp stem cell through lysophosphatidic acid receptor 3/extracellular signal-regulated kinase signaling axis. J Dent Sci. 2023;18(3):1219-26. (**IF: 3.4**)
8. Lin KH, Lee SC, Dacheux MA, **Norman DD**, Balogh A, Bavaria M, Lee H, Tigyi G. E2F7 drives autotaxin/Enpp2 transcription via chromosome looping: Repression by p53 in murine but not in human carcinomas. FASEB J. 2023;37(7):e23058. (**IF: 4.4**)
9. Banerjee S, Lee S, **Norman DD**, Tigyi GJ. Designing Dual Inhibitors of Autotaxin-LPAR GPCR Axis. Molecules. 2022;27(17). (**IF: 4.6**)
10. Dacheux MA, Lee SC, Shin Y, **Norman DD**, Lin KH, E S, Yue J, Benyo Z, Tigyi GJ. Prometastatic Effect of ATX Derived from Alveolar Type II Pneumocytes and B16-F10 Melanoma Cells. Cancers (Basel). 2022;14(6). (**IF: 5.2**)
11. Lee SC, Lin KH, Balogh A, **Norman DD**, Bavaria M, Kuo B, Yue J, Balazs L, Benyo Z, Tigyi G. Dysregulation of lysophospholipid signaling by p53 in malignant cells and the tumor microenvironment. Cell Signal. 2021;78:109850. (**IF: 4.85**)
12. Tigyi G, Dacheux MA, Lin KH, Yue J, **Norman D**, Benyo Z, Lee SC. Anti-cancer strategies targeting the autotaxin-lysophosphatidic

acid receptor axis: is there a path forward? Cancer Metastasis Rev. 2021;40(1):3-5.
13. Banerjee S, **Norman DD**, Deng S, Fakayode SO, Lee SC, Parrill AL, Li W, Miller DD, Tigyi GJ. Molecular modelling guided design, synthesis and QSAR analysis of new small molecule non-lipid autotaxin inhibitors. Bioorg Chem. 2020;103:104188. (**IF: 5.275**)
14. Lee SC, Dacheux MA, **Norman DD**, Balazs L, Torres RM, Augelli-Szafran CE, Tigyi GJ. Regulation of Tumor Immunity by Lysophosphatidic Acid. Cancers (Basel). 2020;12(5). (**IF: 6.639**)
15. Morstein J, Dacheux MA, **Norman DD**, Shemet A, Donthamsetti PC, Citir M, Frank JA, Schultz C, Isacoff EY, Parrill AL, Tigyi GJ, Trauner D. Optical Control of Lysophosphatidic Acid Signaling. J Am Chem Soc. 2020;142(24):10612-6. (**IF: 15.419**)
16. Flammier S, Peyruchaud O, Bourguillault F, Duboeuf F, Davignon JL, **Norman DD**, Isaac S, Marotte H, Tigyi G, Machuca-Gayet I, Coury F. Osteoclast-Derived Autotaxin, a Distinguishing Factor for Inflammatory Bone Loss. Arthritis Rheumatol. 2019;71(11):1801-11. (**IF: 9.586**)
17. Morstein J, Hill RZ, Novak AJE, Feng S, **Norman DD**, Donthamsetti PC, Frank JA, Harayama T, Williams BM, Parrill AL, Tigyi GJ, Riezman H, Isacoff EY, Bautista DM, Trauner D. Optical control of sphingosine-1-phosphate formation and function. Nat Chem Biol. 2019;15(6):623-31. (**IF: 12.587**)
18. Tigyi GJ, Yue J, **Norman DD**, Szabo E, Balogh A, Balazs L, Zhao G, Lee SC. Regulation of tumor cell - Microenvironment interaction by the autotaxin-lysophosphatidic acid receptor axis. Adv Biol Regul. 2019;71:183-93.
19. Tigyi GJ, Johnson LR, Lee SC, **Norman DD**, Szabo E, Balogh A, Thompson K, Boler A, McCool WS. Lysophosphatidic acid type 2 receptor agonists in targeted drug development offer broad therapeutic potential. J Lipid Res. 2019;60(3):464-74. (**IF: 4.483)**
20. Banerjee S, **Norman DD**, Lee SC, Parrill AL, Pham TC, Baker DL, Tigyi GJ, Miller DD. Highly Potent Non-Carboxylic Acid Autotaxin Inhibitors Reduce Melanoma Metastasis and Chemotherapeutic Resistance of Breast Cancer Stem Cells. J Med Chem. 2017;60(4):1309-24. (**IF: 6.253**)

21. Ragle LE, Palanisamy DJ, Joe MJ, Stein RS, **Norman DD**, Tigyi G, Baker DL, Parrill AL. Discovery and synthetic optimization of a novel scaffold for hydrophobic tunnel-targeted autotaxin inhibition. Bioorg Med Chem. 2016;24(19):4660-74. (**IF: 2.930**)
22. Balogh A, Shimizu Y, Lee SC, **Norman DD**, Gangwar R, Bavaria M, Moon C, Shukla P, Rao R, Ray R, Naren AP, Banerjee S, Miller DD, Balazs L, Pelus L, Tigyi G. The autotaxin-LPA2 GPCR axis is modulated by gamma-irradiation and facilitates DNA damage repair. Cell Signal. 2015;27(9):1751-62. (**IF: 4.191**)
23. Lee SC, Fujiwara Y, Liu J, Yue J, Shimizu Y, **Norman DD**, Wang Y, Tsukahara R, Szabo E, Patil R, Banerjee S, Miller DD, Balazs L, Ghosh MC, Waters CM, Oravecz T, Tigyi GJ. Autotaxin and LPA1 and LPA5 receptors exert disparate functions in tumor cells versus the host tissue microenvironment in melanoma invasion and metastasis. Mol Cancer Res. 2015;13(1):174-85. (**IF: 4.510**)
24. Patil R, Szabo E, Fells JI, Balogh A, Lim KG, Fujiwara Y, **Norman DD**, Lee SC, Balazs L, Thomas F, Patil S, Emmons-Thompson K, Boler A, Strobos J, McCool SW, Yates CR, Stabenow J, Byrne GI, Miller DD, Tigyi GJ. Combined mitigation of the gastrointestinal and hematopoietic acute radiation syndromes by an LPA2 receptor-specific nonlipid agonist. Chem Biol. 2015;22(2):206-16. (**IF: 5.774**)
25. Fells JI, Lee SC, **Norman DD**, Tsukahara R, Kirby JR, Nelson S, Seibel W, Papoian R, Patil R, Miller DD, Parrill AL, Pham TC, Baker DL, Bittman R, Tigyi G. Targeting the hydrophobic pocket of autotaxin with virtual screening of inhibitors identifies a common aromatic sulfonamide structural motif. FEBS J. 2014;281(4):1017-28. (**IF: 4.001**)
26. Leblanc R, Lee SC, David M, Bordet JC, **Norman DD**, Patil R, Miller D, Sahay D, Ribeiro J, Clezardin P, Tigyi GJ, Peyruchaud O. Interaction of platelet-derived autotaxin with tumor integrin alphaVbeta3 controls metastasis of breast cancer cells to bone. Blood. 2014;124(20):3141-50. (**IF: 10.452**)
27. Morales-Lazaro SL, Serrano-Flores B, Llorente I, Hernandez-Garcia E, Gonzalez-Ramirez R, Banerjee S, Miller D, Gududuru V, Fells J, **Norman D**, Tigyi G, Escalante-Alcalde D, Rosenbaum T. Structural

determinants of the transient receptor potential 1 (TRPV1) channel activation by phospholipid analogs. J Biol Chem. 2014;289(35):24079-90. (**IF: 4.573**)

28. Patil R, Fells JI, Szabo E, Lim KG, **Norman DD**, Balogh A, Patil S, Strobos J, Miller DD, Tigyi GJ. Design and synthesis of sulfamoyl benzoic acid analogues with subnanomolar agonist activity specific to the LPA2 receptor. J Med Chem. 2014;57(16):7136-40. (**IF: 5.447**)
29. Fells JI, Lee SC, Fujiwara Y, **Norman DD**, Lim KG, Tsukahara R, Liu J, Patil R, Miller DD, Kirby RJ, Nelson S, Seibel W, Papoian R, Parrill AL, Baker DL, Bittman R, Tigyi G. Hits of a high-throughput screen identify the hydrophobic pocket of autotaxin/lysophospholipase D as an inhibitory surface. Mol Pharmacol. 2013;84(3):415-24. (**IF: 4.120**)
30. **Norman DD**, Ibezim A, Scott WE, White S, Parrill AL, Baker DL. Autotaxin inhibition: development and application of computational tools to identify site-selective lead compounds. Bioorg Med Chem. 2013;21(17):5548-60. (**IF: 2.951**)
31. Ren F, Bhana S, **Norman DD**, Johnson J, Xu L, Baker DL, Parrill AL, Huang X. Gold nanorods carrying paclitaxel for photothermal-chemotherapy of cancer. Bioconjug Chem. 2013;24(3):376-86. (**IF: 4.821**)
32. Bolen AL, Naren AP, Yarlagadda S, Beranova-Giorgianni S, Chen L, **Norman D**, Baker DL, Rowland MM, Best MD, Sano T, Tsukahara T, Liliom K, Igarashi Y, Tigyi G. The phospholipase A1 activity of lysophospholipase A-I links platelet activation to LPA production during blood coagulation. J Lipid Res. 2011;52(5):958-70. (**IF: 5.559**)
33. Kramer C, Nahmias Z, **Norman DD**, Mulvihill TA, Coons LB, Cole JA. Dermacentor variabilis: regulation of fibroblast migration by tick salivary gland extract and saliva. Exp Parasitol. 2008;119(3):391-7. (**IF: 1.751**)