BIOGRAPHICAL SKETCH

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NAME: McCormick, Craig

eRA COMMONS USER NAME: CRAIGMCCORMICK

POSITION TITLE: Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
University of New Brunswick, Fredericton, Canada	BSc	05/1995	Biochemistry
University of British Columbia, Vancouver, Canada	PhD	05/2000	Virology
University of California, San Francisco, San Francisco, CA	Postdoctoral Fellow	06/2006	Virology

A. PERSONAL STATEMENT

Research in the McCormick lab is focused on understanding host antiviral stress responses (e.g. autophagy, stress granules) and the tactics employed by viruses to overcome these defenses. We are primarily focused on two viruses: influenza A virus and a cancer-causing herpesvirus known as KSHV.

Influenza A virus (IAV): Influenza A virus (IAV) polymerase complexes function in the nucleus of infected cells, generating mRNAs that bear 5' caps and poly(A) tails which are exported to the cytoplasm and translated by host machinery. Host antiviral defenses include mechanisms that detect the stress of virus infection and arrest cap-dependent mRNA translation, which normally results in the formation of cytoplasmic aggregates of translationally stalled mRNA-protein complexes known as stress granules (SGs). We discovered that IAV encodes three proteins, NS1, NP, and PA-X, which prevent SG formation. Ongoing work is focused on detailed characterization of the mechanism of action of these viral countermeasures. Interestingly, we identified a window of opportunity early in infection when the virus is quite sensitive to stress-induced translation arrest and SG formation. By better understanding these virus-host interactions, we hope to identify new host-directed targets for therapeutic intervention. Together with collaborator Dr. Marta Gaglia and her group, we have discovered fundamental molecular mechanisms of PA-X host shutoff.

Kaposi's sarcoma-associated herpesvirus (KSHV): Our KSHV program encompasses two distinct phases of the infectious cycle, latency and lytic replication. **LATENCY:** Acute oncogenic stress can activate autophagy and facilitate permanent arrest of the cell cycle through a failsafe mechanism known as oncogene-induced senescence (OIS). We discovered that tandemly expressed KSHV v-cyclin and v-FLIP proteins coordinate an attack on OIS. v-cyclin deregulates the cell cycle, triggers DDRs and, if left unchecked, can promote autophagy and senescence. However, during latency v-FLIP blocks v-cyclin-induced autophagy and senescence. Together, these data reveal a coordinated viral gene expression program that usurps autophagy, blocks senescence and facilitates the proliferation of KSHV-infected cells. **LYTIC REPLICATION:** A hallmark of Kaposi's sarcoma is the elaboration of pro-inflammatory cytokines and angiogenic factors by KSHV-infected endothelial cells (ECs). We discovered the mechanisms whereby KSHV proteins increase the production of these host factors by stabilizing the AU-rich-element-containing mRNAs that encode them. We demonstrated that signal transduction pathways subverted by these viral proteins are central nodes of control for stress responses, cytoskeletal dynamics, cell migration and secretion. These proteins are likely key contributors to viral reprogramming of ECs, capable of eliciting many of the phenotypes characteristic of KS tumor cells, and strongly contributing to the post-transcriptional control of EC gene expression and secretion. Ongoing work is focused on understanding how host stress responses affect reactivation from latency, translation of viral proteins, viral replication and release of infectious progeny.

B. POSITIONS AND HONORS

Positions and Employment

2006 - 2013 Assistant Professor, Department of Microbiology & Immunology, DALHOUSIE UNIVERSITY
2013 - 2016 Associate Professor, Department of Microbiology & Immunology, DALHOUSIE UNIVERSITY
2016 – Professor, Department of Microbiology & Immunology, DALHOUSIE UNIVERSITY

2017 – Associate Director, Discovery Research, Canadian Centre for Vaccinology

Other Experience and Professional Memberships

2017 - current Editorial Board Member, *Biochemistry and Cell Biology*
2015 - current Editorial Board Member, *Viruses*
2016 Co-Founder, Canadian Society for Virology

Honors

2007-2012 Canadian Institutes of Health Research New Investigator Salary Award
2018 Lecturer of the Year (selected by undergraduate Microbiology & Immunology students)
2019 Rosemary Gill Award (recognition of outstanding service to students, beyond teaching)

Supervisory Record (13 years)

First 3 Postdoctoral Fellows are all now independent PIs.
18 Graduate Students – including Drew Leidal, PhD: FoM Excellence in Research Award; CIHR-Institute of Cancer Research Publication Prize 2012 (awarded to the top 5 cancer research publications nationwide); Banting Postdoctoral Award 2015-2017

C. Contribution to Science

1. Discovered the mechanism whereby influenza virus prevents infected host cells from stalling translation and forming cytoplasmic stress granules. In response to a variety of stresses, mammalian cells reprogram their translational machinery; translation of mRNAs encoding the bulk of constitutively expressed 'housekeeping' proteins is stalled, and these stalled mRNAs nucleate discrete cytoplasmic foci known as stress granules. We discovered that influenza A virus is subject to restriction by stress granules, and the virus deploys three proteins, NS1, NP and PA-X, that block stress granule formation by distinct mechanisms. Ongoing collaborative studies with the lab of Dr. Marta Gaglia are revealing the mechanism of action of PA-X host shutoff via selective destruction of Pol II transcripts in the cell nucleus (funded by CIHR MOP-84554 and MOP-136817; and NIH R01 award to Dr. Gaglia).
   a. Khaperskyy DA, Hatchette TF, **McCormick C**. (2012) Influenza A virus inhibits cytoplasmic stress granule formation. *FASEB J*. 26(4):1629-39. PMID: 22202676
   b. Khaperskyy DA, Emara MM, Johnston BP, Anderson P, Hatchette TF, **McCormick C**. Influenza A virus blocks antiviral stress-induced translation arrest. *PLoS Pathogens* 10(7):e1004217. PMID: 25010204 PMCID: PMC4092144
   c. Khaperskyy DA*, Schmaling S*, Larkins-Ford J, **McCormick C#**, Gaglia MM#. (2016) Selective degradation of host RNA polymerase II transcripts by influenza A virus PA-X host shutoff protein. *PLoS Pathogens,* 12(2):e1005427 (*co-first authors, # = co-corresponding authors) PMID: 26849127 PMCID: PMC4744033
   d. **McCormick C***, Khaperskyy DA. (2017) Translation inhibition and stress granules in the control of the antiviral immune response. *Nat. Rev. Immunol.* 17(10):647-60. Review. PMID: 28669985
   e. Gaucherand L*, Porter BK*, Levene RE, Price EL, Schmaling SK, Rycroft CH, Kevorkian Y, **McCormick C#**, Khaperskyy DA#, Gaglia MM#. (2019) The influenza A virus endoribonuclease PA-X usurps host mRNA processing machinery to limit host gene expression. *Cell Reports* 27(3):776-792. (* = co-first authors, # = co-corresponding authors) PMID: 30995476

2. Discovered mechanisms whereby KSHV activates unfolded protein response (UPR) sensors but suppresses downstream transcriptional responses to support lytic replication. The UPR resolves ER stress by putting the brakes on synthesis of many proteins, while signaling to the nucleus to turn on a program that aims to correct this imbalance. We discovered that as KSHV replication progresses, all three known UPR sensor proteins, IRE1, ATF6 and PERK, are activated, which is required for efficient viral replication. Normally, activation of each of these three sensor proteins communicates a unique signal to the cell nucleus to stimulate the production of ER stress mitigating proteins, but in KSHV lytic replication all downstream communication is stymied. The failure to resolve ER stress would normally be expected to put

the virus at a disadvantage, but we demonstrated that reversal of this scenario is worse; when we add extra XBP1s to the system to artificially stimulate the production of UPR responsive genes, virus replication is blocked at a late stage and no progeny viruses are released from infected cells. Taken together, these observations suggest that KSHV requires UPR sensor protein activation to replicate but has dramatically altered the outcome to prevent the synthesis of new UPR proteins and sustain stress in the ER compartment. Remarkably, we also observed that viral protein synthesis proceeds efficiently in the face of cellular stress that would normally be expected to arrest bulk translation. The accumulating evidence suggests that herpesvirus mRNA translation can be initiated in an eIF4F-independent manner by an alternative mTORC1/4EBP1-resistant initiation complex, thereby facilitating translation of viral mRNA and the production of infectious progeny. (funded by CIHR MOP-84554)

a. Johnston BP, **McCormick C**. KSHV activates unfolded protein response sensors but suppresses downstream transcriptional responses to support lytic replication (in review, pre-print published in *BioRxiv*)

b. Pringle ES, Robinson CA, **McCormick C**. KSHV lytic replication interferes with mTORC1 regulation of autophagy and viral protein synthesis (*J. Virol.,* in press)

3. Discovered how a tumour virus evades the host senescence response, allowing the continued proliferation of infected cells. Acute oncogenic stress can activate autophagy and facilitate permanent arrest of the cell cycle through a failsafe mechanism known as oncogene-induced senescence (OIS). We discovered that the tandemly-expressed KSHV v-cyclin and v-FLIP proteins coordinate an attack on OIS. v-cyclin deregulates the cell cycle, triggers DDRs and, if left unchecked, can promote autophagy and senescence. However, during latency v-FLIP blocks v-cyclin-induced autophagy and senescence. Together, these data reveal a coordinated viral gene expression program that usurps autophagy, blocks senescence and facilitates the proliferation of KSHV-infected cells. (funded by CIHR MOP-84554)

   a. Leidal AM, Cyr DP, Hill RJ, Lee PWK, **McCormick C**. (2012) Subversion of autophagy by Kaposi's sarcoma-associated herpesvirus impairs oncogene-induced senescence. *Cell Host Microbe*, 11:167-80. PMID: 22341465

4. Discovered the function of two Kaposi's sarcoma-associated herpesvirus (KSHV) proteins that block turnover of labile AU-rich mRNAs that encode pro-inflammatory cytokines and angiogenic factors. A hallmark of Kaposi's sarcoma is the elaboration of pro-inflammatory cytokines and angiogenic factors by KSHV-infected endothelial cells (ECs). I discovered the mechanisms whereby two KSHV proteins, Kaposin B (KapB) and viral G-protein-coupled receptor (vGPCR), increase the production of these host factors by stabilizing the AU-rich-element-containing mRNAs that encode them. I demonstrated that signal transduction pathways subverted by these viral proteins are central nodes of control for stress responses, cytoskeletal dynamics, cell migration and secretion. These observations position KapB and v-GPCR as key contributors to viral reprogramming of ECs, capable of eliciting many of the phenotypes characteristic of KS tumor cells, and strongly contributing to the post-transcriptional control of EC gene expression and secretion. (Funded by CIHR MOP-84554)

   a. **McCormick C,** Ganem D. (2005) The kaposin B protein of KSHV activates the p38/MK2 pathway and stabilizes cytokine mRNAs. *Science* 307:739-41. PMID: 15692053

   b. Corcoran JA, Khaperskyy DA, Johnston B, King CA, Cyr DP, Olsthoorn AV, **McCormick C.** (2012) Kaposi's sarcoma-associated herpesvirus G-protein coupled receptor prevents AU-rich element-mediated mRNA decay. *J. Virol.* 86(16):8859-71. PMID: 22696654 PMCID: PMC3421767

   c. Corcoran JA, Johnston BP, **McCormick C**. (2015) Viral activation of MK2-hsp27-p115RhoGEF-RhoA signaling axis causes cytoskeletal rearrangements, p-body disruption and ARE-mRNA stabilization. *PLoS Pathog* 11(1): e1004597. PMID: 25569678 PMCID: PMC4287613

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Complete List of Published Work in My Bibliography:
https://www.ncbi.nlm.nih.gov/myncbi/1voxkP-z4J9Qo/bibliography/public/

D. RESEARCH SUPPORT (current operating funds only)

2014/09/01-2019/08/30
Canadian Institutes of Health Research (CIHR) Operating Grant
McCormick, Craig (PI)
Stress responses and the control of influenza virus infection
Stress-induced translational arrest represents an important form of antiviral host defense that influenza viruses must overcome to translate viral gene products. The aim of this project is to identify and characterize influenza virus proteins that undermine host antiviral stress responses.
Role: PI

2016/09/01-2021/08/30
Canadian Institutes of Health Research (CIHR) Operating Grant
McCormick, Craig (PI)
Discovery and preclinical development of novel stress granule-inducing antiviral drugs
The goal of this study is to elucidate the mechanism of action of novel host-targeted anti-influenza virus small molecules that selectively induce antiviral stress granules in infected cells.
Role: PI (M. Roberge, D. Khaperskyy, Co-Investigators)

2018/07/01-2023/06/30
NIH R01
Molecular mechanism of action of the influenza A virus PA-X host shutoff protein
The goal of this study is to elucidate the molecular mechanism of action of the PA-X host shutoff protein
Role: Subcontractor (M. Gaglia, PI)

2019/04/01-2024/03/30
Natural Sciences and Engineering Research Council of Canada (NSERC) – Discovery Grant
McCormick, Craig (PI)
Synthetic herpesvirus genomes with an expanded genetic code
Role: PI