BIOGRAPHICAL SKETCH

NAME: Maryam Yousefi

eRA COMMONS USER NAME (credential, e.g., agency login): YOUSEFIMARYAM

POSITION TITLE: Postdoctoral Fellow

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Tehran (Tehran, Iran)	B.Sc.	02/2009	Biotechnology
University of Tehran (Tehran, Iran)	M.Sc.	06/2011	Medical Biotechnology
University of Pennsylvania (Philadelphia, PA)	Ph.D.	08/2017	Cell and Molecular Biology
Stanford University (Stanford, CA)	Postdoc	09/2017-present	Genetics/Cancer Biology

A. Personal Statement

My ultimate goal is to become an independent principal investigator focusing on development of novel mechanistic-based preventive and therapeutic interventions with minimal adverse side-effects for cancer patients. During my Ph.D., I demonstrated the necessity of tight regulation of Musashi family of RNA-binding proteins and metabolic pathways in the stem cell compartment of the intestinal epithelium, the most highly proliferative tissues in mammals, during regeneration and oncogenesis (Li et al, ***Cell Report*** 2015; Wang et al., ***Nature Communication*** 2015; Yousefi et al., ***Journal of Cell Biology*** 2016). I went on to regulate these pathways using nutrient modulation and calorie restriction in order to prevent damage to highly proliferative tissues in response to injuries frequently caused by conventional cancer treatments such as radiotherapy (Yousefi et al., *Under consideration*). My project in Dr. Winslow's laboratory is focused on generating large-scale pharmacogenomic maps of lung cancer through integration of genetically-engineered mouse models, CRISPR-based somatic genome engineering, and quantitative genomics and mathematical modeling. With my experience in stem cell and regenerative biology, Dr. Winslow's extensive experience in cancer biology and development of quantitative screening technologies, and substantial interdisciplinary collaboration opportunities at Stanford University I will be poised to become an independent scientist focusing on development of efficient and safe cancer therapy.

B. Positions and Honors

Positions

2017-present Postdoctoral Fellow, Stanford University School of Medicine, Department of Genetics, Laboratory of Dr. Monte M. Winslow

2011-2017 PhD, University of Pennsylvania, Department of Biomedical Sciences, Philadelphia, PA, Laboratory of Dr. Christopher J. Lengner

2009-2011 Research Assistant, Royan Institute for Stem Cell Biology and Technology. Tehran, Iran, Laboratories of Dr. Hossein Baharvand and Dr. Ghassem Hosseini Salekdeh

Awards and Honors

2013-2016 Howard Hughes Medical Institute International Student Fellowship
2015 Best poster award, University of Pennsylvania, Department of Biomedical Sciences Research Retreat
2014 Best poster award, University of Pennsylvania, 18th Annual Cell and Molecular Biology Symposium

C. Contributions to Science

1. Understanding the underlying mechanism of radiosensitivity and repair in the gastrointestinal tract

Radiation and chemotherapy remain the most effective and widely used cancer treatments. These treatments cause DNA damage and selectively target rapidly proliferating cells such as cancer cells, as well as inevitably cause damage to normal tissues, particularly those undergoing rapid self-renewal. The side effects associated with radiation and chemotherapy are most pronounced in the gastrointestinal tract and hematopoietic system. These tissues are fast renewing and have a stem cell compartment that plays an essential role in homeostasis, and in repair following injury. Intestinal homeostasis and regeneration after injury such as radiation-induced acute gastrointestinal syndrome are governed by a two-stem cell system (Li et al., Stem Cell Reports 2014; Li et al., Developmental Dynamics 2016; Yousefi et al., Trends in Cell Biology 2017). This system includes a slow-cycling radioresistant reserve stem cell that gives rise to a rapidly cycling crypt base columnar stem (CBC) characterized by high canonical Wnt pathway activity. The active CBC fuels normal intestinal homeostasis, and high dose gamma irradiation (above 10Gy) quantitatively ablates Wnt^{high} CBCs, driving the reserve stem cells to proliferate and regenerate the epithelium (Yousefi et al., Journal of Cell Biology 2016).

We demonstrated that stimulation of the Akt-mTORC1 axis activates these reserve stem cells and that activity of the Msi RNA binding protein upstream of mTORC1 is sufficient to drive this process. In the absence of Msi activity, reserve ISCs failed to enter cell cycle, and following high-dose γ-radiation injury, this resulted in failed epithelial regeneration. Remarkably, reserve ISC activation and epithelial regeneration after injury could be rescued by mTORC1 stimulation with dietary modulation. In addition, we showed that promiscuous activation of the reserve stem cells through activation of Msi or dietary modulation rendered them susceptible to high dose gamma irradiation. Consistently, calorie restriction or pharmacological repression of mTORC1 signaling at the time of injury protected the tissue stem cells form radiation-induced injury (Yousefi et al. Journal of Cell Biology 2016; Yousefi et al., under consideration). These data inform clinical strategies based on modulation of Msi-mTORC1 axis to prevent off-target damages caused by chemo- and radiotherapy.

1. **Yousefi M**, Berry C, Li N, Schoenberger J, Simeonov K, , Nakauka-Ddamba A, Jensen S, Lengner C. "Calorie restriction governs regeneration of the intestinal epithelium through cell-autonomous regulation of mTORC1 in reserve stem cells. " ***Under consideration***
2. Cedeno RJ, Nakauka-Ddamba A, **Yousefi M**, Sterling S, Leu NA, Li N, Pehrson JR, Lengner CJ. "The histone variant macroH2A confers functional robustness to the intestinal stem cell compartment." **PLoS One**. 2017 Sep 21;12(9):e0185196.
3. **Yousefi M**, Li N, Nakauka-Ddamba A, Wang S, Yu Z, Parada K, Jensen S, Kharas M, and Lengner C. "Msi RNA binding proteins control intestinal stem cell quiescence." ***Journal of Cell Biology***, 2016 Nov 7;215(3):401-413.
4. **Yousefi M**, Li L, and Lengner C. "Hierarchy and plasticity in the intestinal stem cell compartment." ***Trends in Cell Biology***, 2017 Oct;27(10):753-764.
5. Li N*, **Yousefi M***, Nakauka-Ddamba A*, Tobias JW, Jensen ST, Morrisey EE, Lengner C. "Heterogeneity in readouts of canonical Wnt pathway activity within intestinal crypts." ***Developmental Dynamics***, 2016 Aug; 245(8):822-33. *equally contributing authors
6. Li N, **Yousefi M**, Nakauka-Ddamba A, Jain R, Tobias J, Epstein JA, Jensen ST, Lengner C. "Single-cell analysis of proxy reporter allele-marked epithelial cells establishes intestinal stem cell hierarchy." Stem ***Cell Reports***, 2014 Nov; 3(5):876-91.

2. Transformation of the intestinal epithelium by the Musashi RNA binding proteins

The Musashi RNA-binding proteins are potent oncogenes playing key roles in haematopoietic stem cell homeostasis and malignant haematopoiesis. We demonstrated that Musashi is expressed in the intestinal stem cell compartment, that its expression is elevated in colorectal adenocarcinomas, and that Musashi loss-of-function abrogates colorectal cancer cell growth. Musashi gain-of-function in the intestinal epithelium in a drug-inducible mouse model is sufficient to phenocopy many of the morphological and molecular consequences of acute loss of the APC tumor suppressor in the intestinal epithelium in a Wnt-independent manner. Transcriptome-wide RNA-binding analysis indicates that Musashi acts as a pleiotropic inhibitor of known intestinal tumor suppressors including Lrig1, Bmpr1a, Cdkn1a and Pten. Finally, we demonstrated that inhibition of the PDK-AKT-mTORC1 axis rescues oncogenic consequences of Musashi induction. Taken together, our findings identified Musashi as a central component in an unappreciated oncogenic pathway promoting intestinal transformation (Li et al., Cell Reports 2015; Wang et al., Nature Communication 2015)

1. Li N, **Yousefi M**, Parada K, Nakauka-Ddamba A, Li F, Wang S, Naqvi A, Rao S, Tobias J, Minuesa G, Barlowe T, Valvezan A, Shankar S, Deering R, Klein P, Jensen S, Kharas M, Gregory B, Yu Z, and Lengner C. "The Msi family of RNA-binding proteins function redundantly as intestinal oncoproteins." ***Cell Reports***, 2015 Dec 22; 13(11):2440-55.
2. Wang S, Li N, **Yousefi M**, Nakauka-Ddamba A., Li F, Parada K, Rao S, Minuesa G., Katz Y, Gregory BD, Kharas M, Yu Z, Lengner, C. "Transformation of the intestinal epithelium by the MSI2 RNA binding protein." ***Nature Communications***, 2015 Mar; 16;6:6517.

3. Finding accessible and abundant sources of cells for cell-based therapy

Stem cells have a remarkable potential to develop into many different cell types in the body during early life and growth (Yousefi et al, Stem Cell Reviews and Reports 2012). Given their unique regenerative abilities, stem cells offer new potentials in many different areas of research and therapy. Human embryonic and induced pluripotent stem cells offer a platform technology with the potential for developmental biology and cell-based therapy. We developed a robust and cost-effective way for mass production of these cells, which is required for their clinical application in cell-based therapy, in suspension for an extended period of time (Baharvand et al., Human Embryonic Stem Cells Handbook 2012; Rezaei Larijani et al., Stem Cells and Development 2011). In another work, we tested the potential of terminally differentiated cells into insulin producing β cells. Destruction or dysfunction of pancreatic β cells is associated with type 1 and type 2 diabetes. We could convert intestinal crypts into insulin producing cells *in vivo* with features of β cells. Our results demonstrated that the intestine is an accessible and abundant source for production of functional insulin-producing cells.

1. **Yousefi M**, Hajihoseini V, Jung W, Hosseinpour B, Rassouli H, Lee B, Baharvand H, Lee K, Salekdeh GH. "Embryonic stem cell interactomics: the beginning of a long road to biological function." ***Stem Cell Reviews and Reports***, 8(4):1138-54. 2012.
2. Baharvand H, Larijani MR, **Yousefi M**. "Protocol for expansion of undifferentiated human embryonic and pluripotent stem cells in suspension." ***Human Embryonic Stem Cells Handbook***, 873:217-26, 2012.
3. Rezaei Larijani M, Seifinejad A, Pournasr B, Hajihoseini V, Hassani SN Totonchi, M, **Yousefi M**, Shamsi F, Hosseini Salekdeh G, Baharvand H. "Long-term maintenance of undifferentiated human embryonic and induced pluripotent stem cells in suspension." ***Stem Cells and Development***, 20(11):1911-23, 2011.
4. Chen YjJ, Finkbeiner SR, Weinblatt D, Emmett MJ, Tameire F, **Yousefi M**, Yang C, Maehr R, Zhou Q, Shemer R, Dor Y, Li C, Spence JR, Stanger B. "De novo formation of insulin-producing "neo-beta cell islets" from intestinal crypts." **Cell Reports**, 2014 Mar. 6(6): p. 1046-58.

D. Additional Information: Research Support and/or Scholastic Performance

Completed Research Support

Howard Hughes Medical Institute International Student Fellowship (59107993), 09/2013- 09/2016