BIOGRAPHICAL SKETCH

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NAME: Zhaohui Feng

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

POSITION TITLE: Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Zhejiang University School of Medicine, Hangzhou, China	M.D.	07/1993	Clinical Medicine
Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China	Intern	06/1993	Clinical Medicine
Zhejiang University School of Medicine, Hangzhou, China	Ph.D.	11/1998	Molecular Cancer Biology
New York University School of Medicine, New York	Postdoc	08/2003	Molecular Cancer Biology
University of Medicine and Dentistry of New Jersey (UMDNJ), New Jersey	Postdoc	06/2007	Molecular Cancer Biology

A. Personal Statement

Tumor suppressor p53 plays a key role in tumor suppression. To ensure the proper levels and functions of p53 in tumor suppression, p53 is tightly regulated by different mechanisms in cells. Many tumor-associated mutant p53 proteins not only lose the tumor suppressive function of wild-type p53, but also gain new activities in promoting tumorigenesis, which is defined as mutant p53 gain-of-function (GOF). We have long-standing interest and expertise in studying p53 signaling pathway and GOF mutant p53 in cancer. We are interested in identifying new regulators and regulation mechanisms for p53 and mutant GOF p53 and their signaling pathways, such as new E3 ubiquitin ligases, microRNAs and SUMOylation modification that regulate p53 and its signaling pathway. Metabolic reprogramming has been regarded as a hallmark of tumor cells and a key contributor to malignant progression. The role of p53 and other tumor suppressors in regulating cellular metabolism and how this contributes to tumor suppression are not fully understood. We are interested in studying how p53 and GOF mutant p53 and other tumor suppressors regulate metabolism to impact tumorigenesis, and how metabolic changes in cancer can be targeted for therapy.

Ongoing and recently completed projects that I would like to highlight include:

NIH/NCI R01CA214746
PI: Z. Feng
7/2018 –6/2024
SENP6, a novel p53 negative regulator, is an important new player in cancer

NIH/NCI R01 CA229257
PI: Z. Feng

7/2021-6/2026
The regulation of mutant p53 protein accumulation in cancer: molecular basis and therapeutic potential

NIH/NCI 1R01CA227912
PI: Z. Feng /W. Hu
3/2018-2/2024
Metabolic reprogramming in Breast Cancer

NIH/NCI 1R01CA260837-01
PI: W. Hu/Z. Feng, Zhaohui
4/2021 – 3/2026
The mechanism of mutant p53 gain-of-function in colorectal cancer

Citations:

a. Liu J, Zhang C, Wu H, Sun X, Li X, Huang S, Yue X, Lu Z, Shen Z, Su X, White E, Haffty BG, Hu W, **Feng Z.** (2020) Parkin ubiquitinates phosphoglycerate dehydrogenase to suppress serine synthesis and tumor progression. ***J. Clin. Invest***. 130(6), 3253-3269. PMCID: PMC7260041

b. Chang C, Wang J, Zhao Y, Liu J, Yang X, Yue X, Wang H, Zhou F, Inclan-Rico J, Ponessa J, Xie P, Zhang L, Siracusa M, **Feng Z** (co-corresponding)**,** Hu W. (2021) Tumor suppressor p53 regulates intestinal type 2 immunity. ***Nature Communications****,* 12(1):3371. PMID: 3409967

c. Liu J, Zhang C, Zhang T, Chang CY, Wang J, Bazile L, Zhang L, Haffty BG, Hu W, **Feng Z**. (2022) Metabolic enzyme LDHA activates Rac1 GTPase as a noncanonical mechanism to promote cancer. ***Nat Metab***. 4(12):1830-1846. PMID: 36536137

d. Liu J, Zhang C, Xu D, Zhang T, Chang CY, Wang J, Zhang L, Haffty BG, Zong W, Hu W, **Feng Z**. (2023) The ubiquitin ligase TRIM21 regulates mutant p53 accumulation and gain-of-function in cancer. ***J. Clin. Invest***. e164354. PMID: 36749630

B. Positions, Scientific Appointments, and Honors

Positions and Employment

7/2020-present	Professor, Department of Radiation Oncology, Department of Pharmacology, Rutgers Cancer Institute of New Jersey, Rutgers, State University of New Jersey
7/2014-6/2020	Associate Professor, Department of Radiation Oncology, Department of Pharmacology, Rutgers Cancer Institute of New Jersey, Rutgers, State University of New Jersey
7/2008-6/2014	Assistant Professor, Department of Radiation Oncology, Department of Pharmacology, Rutgers Cancer Institute of New Jersey, Rutgers, State University of New Jersey
7/2007-6/2008	Instructor, Department of Pediatrics, University of Medicine and Dentistry of New Jersey

Other Experience and Professional Memberships

2023-present: Standing member, NIH BCO study section
2020-2022: Standing member, NIH MONC study section
2020: NIH Special Emphasis Panel R15 study section
2019: NIH/NCI Fellowships study section; NIH/NCI CE study section; DOD breast cancer study section; DOD ovarian cancer study section; National Research Foundation, Singapore; Worldwide Cancer Research, United Kingdom
2018: NIH/NCI CE study section; NIH R15 study section; NIH/NCI MONC study section; NSF, Cellular Dynamics and Function Program
2016: NIH/NCI CAMP study section; NIH/NCI Special Emphasis Panel

2015: NIH/NCI-I Transition to Independence study section; NIH/NCI study section: Research answers to provocative questions; NSF Graduate Research Fellowship Program
2012-2022: DOD breast cancer study section; DOD ovarian cancer study section
2012-2014: International Association of Cancer Research, United Kingdom; US-Israel Binational Science Foundation, Israel; NIH/NCI-I Transition to Independence section; The Parkinson's Disease Association of the United Kingdom; DOD Breast Cancer study section

C. Contributions to Science

1. **Metabolic reprogramming in cancer**. Our studies increase the understanding of the role and mechanism of metabolic reprogramming in cancer. We also found a novel function of E3 ubiquitin ligase CUL3 in regulation of lipid synthesis through degradation of lipogenic enzyme ACLY, which contributes to the function of CUL3 in tumor suppression. We found that E3 ubiquitination ligase Parkin ubiquitinates HIF-1α to suppress glycolsysis, and ubiquitinates phosphoglycerate dehydrogenase (PHGDH) to suppress serine synthesis as novel mechanisms of Parkin in tumor suppression. Recently, we found that metabolic enzyme LDHA, which is frequently overexpressed in cancer, binds and activates small GTPase Rac1 as a noncanonical mechanism to promote cancer progression.

    a. Zhang C, Liu J, Huang G, Zhao Y, Yue X, Wu H, Li J, Zhu J, Haffty BG, Hu W, **Feng Z.** (2016) Cullin3-KLHL25 ubiquitin ligase targets ACLY for degradation to inhibit lipid synthesis and tumor progression. ***Genes Dev***. 30(17):1956-70.
    b. Liu J, Zhang C, Zhao Y, Yue X, Wu H, Huang S, Chen J, Tomsky K, Xie H, Khella K, Gatza M, Xia D, Gao J, White E, Haffty BG, Hu W, **Feng Z.** (2017) Parkin targets HIF-1α for ubiquitination and degradation to inhibit breast tumor progression. ***Nature Communications***. 8(1):1823. PMID:29180628.
    c. Liu J, Zhang C, Wu H, Sun X, Li X, Huang S, Yue X, Lu Z, Shen Z, Su X, White E, Haffty BG, Hu W, **Feng Z.** (2020) Parkin ubiquitinates phosphoglycerate dehydrogenase to suppress serine synthesis and tumor progression. ***J Clin Invest.*** 130(6):3253-3269. (see the commentary in *J Clin Invest*. 2020;130(6): 2820)
    d. Liu J, Zhang C, Zhang T, Chang CY, Wang J, Bazile L, Zhang L, Haffty BG, Hu W, **Feng Z**. (2022) Metabolic enzyme LDHA activates Rac1 GTPase as a noncanonical mechanism to promote cancer. ***Nat Metab.*** 4(12):1830-1846. PMID: 36536137

2. **p53 and its signaling pathway in metabolic regulation**. Our studies contribute to the understanding of the novel function of tumor suppressor p53 in metabolic regulation. It had been widely accepted that the functions of p53 in apoptosis, cell cycle arrest and senescence play a key role in tumor suppression, recent studies including ours have revealed that the function of p53 in metabolic regulation also contributes significantly to the tumor suppressive function of p53. We identified several novel p53 target genes, including GLS2, Parkin, and RRAD, which mediate the function of p53 in metabolic regulation. We found that mutant p53 promotes glycolysis as a novel gain-of-function to promote tumorigenesis, providing a novel mechanism for mutant p53 in promoting tumor progression. Our studies increase the understanding of the role and mechanism of p53 in metabolic regulation and tumor suppression.

    a. Hu W., Zhang C., Wu R., Sun Y. Levine A.J. **Feng Z.** (2010) GLS2, a novel p53 target gene, regulates energy metabolism and antioxidant function***. Proc Natl Acad Sci USA***., 107(16):7455-60. (see the commentary in Nature. 2010;466(7309):905)
    b. Zhang C, Wu R. Lin M. Wang X. Levine AJ., Hu W. **Feng Z.** (2011) Parkin, a novel p53 target gene, mediates the function of p53 in regulating glucose metabolism and the Warburg effect. ***Proc Natl Acad Sci USA.,*** 108(39):16259-64.
    c. Zhang C, Liu L, Liang YJ, Rui W, Lin M, Hong X, Liu L, Levine AJ, Hu W, **Feng Z**. (2013) Tumor-associated mutant p53 drives the Warburg effect. ***Nature Communications.*** 4:2935. PMID: 24343302

d. Zhang C., Liu J., Zhao Y., Yue X., Zhu Y., Wang X., Blanco F., Wu h., Bhanot G, Haffty BG., Hu W., **Feng Z**. (2016) Glutaminase 2 is a novel negative regulator of Rac1 and mediates p53 function in suppressing cancer metastasis. ***eLIFE*****,** 10.7554/eLife.10727. PMID: 26751560

3. **Regulation of mutant p53 "gain-of-function":** Mutant p53 often gains oncogenic functions (gain-of-function, GOF) to promote tumor progression. Mutant p53 protein frequently accumulates to high levels in tumor cells, which is critical for mutant p53 GOF. Currently, the mechanisms for mutant p53 accumulation and GOF are poorly understood. We found that overexpression of tumor-associated MDM2 short isoforms inhibits MDM2 activity to degrade mutant p53 in tumors, leading to mutant p53 protein accumulation. We also identified a novel mutant p53 binding partner, Pontin, which plays an important role in promoting mutant p53 GOF through regulating the transcriptional activity of mutant p53. We found that mutant p53 activates Rac1 through Sumoylation modification to exert its GOF function, providing a potential therapeutic target for tumors carrying GOF mutant p53. Recently, we found that the ubiquitin ligase TRIM21 ubiquitinates and degrades mutant p53 to suppress mutant p53 accumulation and gain-of-function in cancer.

   a. Zheng T, Wang J, Zhao Y, Lin M, Zhang C, Liu L, **Feng Z** (co-corresponding), Hu W. (2013) Spliced MDM2 isoforms promote mutant p53 accumulation and gain-of-function in tumorigenesis. ***Nature Communications.*** 4:2996. PMID: 24356649
   b. Zhao Y, Zhang C, Yue X, Li X, Liu J, Yu H, Belyi VA, Yang Q, **Feng Z** (co-corresponding), Hu W. (2015). Pontin, a new mutant p53 binding protein, promotes gain of function of mutant p53. ***Cell Death & Differ,*** 2015;22(11):1824-36. PMID: 25857266.
   c. Yue X, Zhang C, Zhao Y, Liu J, Lin AW, Tan V, Drake JM, Liu L, Boateng MN, Li J, **Feng Z** (co-corresponding), Hu W. (2017) Gain-of-function mutant p53 activates small GTPase Rac1 through SUMOylation to promote tumor progression. ***Genes & Dev***. 31: 1641-54. PMID: 28947497
   d. Liu J, Zhang C, Xu D, Zhang T, Chang CY, Wang J, Zhang L, Haffty BG, Zong W, Hu W, **Feng Z**. (2023) The ubiquitin ligase TRIM21 regulates mutant p53 accumulation and gain-of-function in cancer. ***J. Clin. Invest***. In press.

4. **Regulation of wild-type p53 and its signaling pathway in normal and tumor cells:** p53 and its signaling pathway are tightly regulated in cells to ensure its proper function in tumor suppression. We found that miR-504 negatively regulates p53 through direct binding to p53 3'-UTR. This is one of the first reports to demonstrate the direct negative regulation of p53 by miRNAs as a mechanism for p53 regulation in cells, which highlights the importance of miRNAs in regulation of the p53 pathway and tumorigenesis. We also found that chronic physiological stress can reduce p53 function in tumor suppression. We identified TRIM32, an E3 ubiquitin ligase, as a novel and an important negative regulator of p53. p53 forms a novel negative feedback loop with TRIM32, which contributes to the tight regulation of p53 levels and function. We also found that LIF negatively regulates p53 and forms a novel negative feedback loop with p53 to suppress p53 function.

   a. Hu W, Chang S. Chan, Rui Wu, Zhang Z, Sun Y, Song J, Levine AJ, **Feng Z.** (2010) Negative Regulation of Tumor Suppressor p53 by microRNA miR-504. ***Mol. Cell,*** 38, 689–699.
   b. **Feng Z**, Liu L, Zhang C, Zheng T, Wang J, Lin M, Wang X, Levine AJ, Hu W. (2012) Chronic restraint stress attenuates p53 function and promotes tumorigenesis. ***Proc Natl Acad Sci U S A.*** 109(18):7013-8
   c. Liu J, Zhang C, Wang X, ly P, Xu-Monette Z, Belyi V, Young KH, Hu W, **Feng Z.** (2014) E3 ubiquitin ligase TRIM32 negatively regulates tumor suppressor p53 to promote tumorigenesis. ***Cell Death & Differ***, 21(11):1792-804
   d. Yu H., Yue X., Zhao Y., Li X., Wu L., Zhang C., Liu Z., Lin K., Xu-Monette Z., Young K., Liu J., Shen Z., **Feng Z**. (co-corresponding), Hu W. (2014) LIF negatively regulates tumor suppressor p53 through Stat3/ID1/MDM2 in colorectal cancers. ***Nature Communications***, 5:5218.

5. **The novel activity of p53 and its signaling pathway in regulation of mTOR, reproduction and immunity**. We found that p53 negatively regulates mTOR signaling to regulate different biological processes, including mTOR-mediated autophagy, which was the first report that p53 regulates autophagy. We found that p53 plays a critical role in embryonic implantation and maternal reproduction through regulation of a novel p53 target, LIF, in both mice and humans. This set of work for the first time demonstrates the important physiological role of p53 and its pathway in reproduction in vertebrates. This discovery could in future form the basis of novel fertility treatments. Recently, we found that LIF inhibits graft-versus-leukemia (GVHD) through regulating host immune response and intestinal stem cell function, which provides a potential strategy for GVHD prevention and therapy. Our recent study also revealed a previously unidentified function of p53 in regulation of type 2 immunity in the gut in response to parasitic infections, demonstrating a critical role of p53 in immune response.

    a. **Feng Z,** Zhang H, Levine AJ, Jin S. (2005) The coordinate regulation of the p53 and mTOR pathways in cells. ***Proc Natl Acad Sci USA****,* 102:8204-8209. PMID: 15928081.
    b. Hu W., **Feng Z** (co-first author), Teresky AK., Levine AJ. (2007) p53 regulates maternal reproduction through LIF. ***Nature;*** 450 (7170): 721-724.
    c. Chang C, Wang J, Zhao Y, Liu J, Yang X, Yue X, Wang H, Zhou F, Inclan-Rico J, Ponessa J, Xie P, Zhang L, Siracusa M, **Feng Z** (co-corresponding)**,** Hu W. (2021) Tumor suppressor p53 regulates intestinal type 2 immunity. ***Nature Communications****,* 12(1):3371. PMID: 34099671
    d. Wang J, Chang CY, Yang X, Zhou F, Liu J, Zhu S, Yu XZ, Liu C, O'Sullivan TE, Xie P, **Feng Z** (co-corresponding), Hu W. (2022) Leukemia inhibitory factor protects against graft-versus-host disease while preserving graft-versus-leukemia activity. ***Blood***, 140(19):2076-2090. PMID: 35981499

Complete List of Published Work in MyBibliography (100 peer-reviewed articles):

http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/47555445/?sort=date&direction=descending