HHS Public Access

Author manuscript

J Cell Biochem. Author manuscript; available in PMC 2020 August 28.

Published in final edited form as:

J Cell Biochem. 2019 July ; 120(7): 10952–10955. doi:10.1002/jcb.28511.

P53: The Endothelium Defender

Mohammad Afaz Uddin[1], **Nektarios Barabutis**[1,*]

[1]School of Basic Pharmaceutical and Toxicological Sciences, College of Pharmacy, University of Louisiana Monroe, Monroe, LA 71201, USA.

P53 represents the paradigm of a multitalented transcription factor, responsible for the cellular defense against a plethora of potentially harmful stimuli. It exercises the ability to strongly oppose both cancer and inflammation, partially due to the fact that both conditions are highly interrelated. Endothelial hyperpermeability is considered the hallmark of severe lung inflammation, and the cardinal feature of the lethal acute respiratory distress syndrome. An emerging body of evidence suggests a strategic role of P53 towards vascular barrier integrity. The "endothelium defender" orchestrates meticulously devised responses; to counteract toxin-induced destructions of endothelial monolayers. The present effort seeks to further our understanding on the expanding P53 universe, discussing the most recent information regarding the involvement of that molecule in the pulmonary function.

The discovery of P53 initiated intense efforts to oppose cancers via the promotion of tumor suppressive activities, although at the onset of its discovery the “Guardian of The Genome” (Lane, 1992) was considered to be an oncogene that promoted malignancies(Levine, 2018). It was soon realized that the oncogenic activities of that molecule were inflicted to the mutant P53 counteracts, abundantly existent in a diverse variety of tumors(Labuschagne, Zani, & Vousden, 2018). More than 50% of human cancers express mutants P53, responsible for malignant transformations and metastasis(Levine, 2017a).

P53 is a transcription factor, devoted to sense a plethora of environmental and cellular stresses. It orchestrates carefully devised molecular responses, in order to counteract a diverse variety of stimuli and prevent cellular dysfunctions. P53 post-translational modifications, such as phosphorylation, acetylation and methylation, may trigger cell cycle arrest or apoptosis (Levine, 2017b). In the instances of less severe circumstances, it initiates mechanisms to repair molecular functions (Tiwari, Jones, & Abrams, 2018).

P53 have been long associated with the suppression of both cancer and inflammation(Barabutis, Schally, & Siejka, 2018). The advanced properties of this “multi-talented” transcription factor, are partially due to the tight association between cancer and inflammation(Bottazzi, Riboli, & Mantovani, 2018). Cancer has been shown to progress more aggressively under severe inflammatory conditions, while such circumstances are ideal

*To whom correspondence should be addressed at: Nektarios Barabutis, M.Sc., Ph.D., School of Basic Pharmaceutical and Toxicological Sciences, College of Pharmacy, University of Louisiana Monroe, Monroe, LA 71201, United States of America, barabutis@ulm.edu, Phone: (318) 342 −1460.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

for malignant transformations(El-Hajjar et al., 2018; Gupta, Kunnumakkara, Aggarwal, & Aggarwal, 2018). The anti-inflammatory properties of that protein have been extensively investigated by numerous groups, and laborious efforts on the investigation of the relevant mechanisms are in progress(Liu, Zeng, Wang, Zheng, & Luan, 2018; Sagiv et al., 2018; Wang et al., 2018; Xue & Li, 2018).

For more than a decade, we investigate the interrelated signaling pathways involved in the progression of both cancer and inflammation(Barabutis & Schally, 2010). We have reported in cancer cells that P53 is involved in the mediation of the anti – oxidant and anti - cancer activities of Growth Hormone Releasing Hormone (GHRH) antagonists(Barabutis & Schally, 2008a). Furthermore, P53 was found to be associated with the anti - inflammatory activities of those compounds in non - cancerous human tissues(Barabutis, Siejka, & Schally, 2011). GHRH antagonists represent one of the most promising therapies against a plethora of cancers. They “sabotage” the growth factor activity of GHRH, and corrupt major signaling cascades that lead to tumor prevalence(Popovics, Cai, Sha, Rick, & Schally, 2018). The in vitro “silencing” of the intrinsic GHRH in the most common human malignancies, virtually stopped their proliferation, which in turn it was restored after supplementation of exogenous GHRH(Barabutis & Schally, 2008b). Currently, the development of those compounds is advanced by prominent leaders on the field of endocrinology and oncology(Mendoza-Valdes, 2015).

Vascular hyperpermeability is associated with carcinogenetic and inflammatory processes. Moreover, it is the hallmark of the most lethal cardiovascular complications, such as the Acute Lung Injury (ALI) and its most severe form, namely the Acute Respiratory Distress Syndrome (ARDS)(Barabutis, Verin, & Catravas, 2016). Unfortunately, ARDS remains one of the main cause of morbidity and mortality in hospitalized patients. The deteriorating consequences of that syndrome are irreversible, since the respiratory function of those patients in need virtually collapses(Nanchal & Truwit, 2018). The pulmonary endothelium becomes dysfunctional, and these patients must be supported by mechanical ventilators due to severe hypoxemia. Due to all those events, the exploration of new therapeutic avenues to fight this devastating pathology, it is of the highest priority in the medical field(Thompson, Chambers, & Liu, 2017).

Hsp90 inhibitors have been long associated with anti-cancer properties, and ongoing trials will evaluate the therapeutic value of those drugs towards malignancies(Barabutis & Catravas, 2015). Those compounds stop the maturation of the plethora of Hsp90 client proteins (kinases, transcription factors), which are key players in the aggression of harmful cellular events(Barabutis et al., 2013). Further, Hsp90 inhibitors exercise the ability to recruit P53, which in turn orchestrates a battery of protective and anti–inflammatory responses against toxin-induced violations of the cellular homeostasis. To the best of our knowledge, on 2015 we were the first to report that P53 expression levels are crucial for the maintenance of the vascular barrier integrity. P53 silencing by siRNA that specifically targets this transcription factor resulted to the severe weakening of the human vascular barrier function.

The transendothelial resistance of those transfected monolayers was dramatically reduced. A similar result was exerted by using the P53 inhibitor Pifithrin. Those human lung

microvascular endothelial cells became much more susceptible to LPS than the relevant control groups. The nutlin - induced P53 induction delivered the opposite effect, thus supported the vascular structure and protected those cells against the barrier destructive and LPS-induced inflammatory events(Barabutis et al., 2015). Indeed, both P53 inhibitors (MDM4 and MDM2) were affected by this toxin, in a manner that resulted to reduced intracellular P53 levels. Similarly to nutlin, Hsp90 inhibitors increased P53 abundance, probably due to the elevated expression of the Hsp90/P53 complexes in the intracellular niche(Barabutis et al., 2015).

In continuation of those studies, we explored the effects of P53 in major regulators of the actomyosin cytoskeleton, namely the Rac1 and RhoA GTPases. The former is responsible for the deactivation of the actin severing activity of cofilin, and the latter is the major transducer of robust inflammatory processes that enacts the formation of F actin fibers. Our observations suggested that P53 can direct the activities of both GTPases, to fight inflammation and support the pulmonary endothelium. It enhances the Rac1 activity to increase the barrier integrity; and/or suppress the RhoA activity to prevent the formation of stress actin fibers, as reflected in the levels of MLC2 phosphorylation(Barabutis, Dimitropoulou, Gregory, & Catravas, 2018).

Since Hsp90 inhibitors induce P53 expression, we decided to test whether those compounds can affect the phosphorylation levels of P53, and whether those post translational modifications have effects on the LPS – induced mice inflammation. Our results indicate that Hsp90 inhibitors suppress inflammation via the prevention of the LPS- inflicted P53 phosphorylation(Barabutis, Uddin, & Catravas, 2018). Those events, in combination with our previous observations in “Super P53” mice”(Barabutis, Dimitropoulou, et al., 2018), conclude that P53 may serve as the “Fire Fighter” of the endothelium. It enhances microvascular barrier integrity; and suppresses the prevalence of inflammation in the pulmonary microvasculature(Barabutis, Uddin, et al., 2018).

In our opinion, P53 represents an underappreciated factor in the field of vascular biology and pharmacology. Further exploration of the activities of that molecule in the vasculature (i.e. use of advanced models of genetically modified mice, exploration of P53 modulators in vascular permeability), will reveal important properties of that transcription factor towards the regulation of the vascular hemostasis and the protection of the lungs against harmful and toxic insults. Most importantly, the discovery of those new regulatory networks will provide new information that may lead to the development of improved pharmacological agents towards inflammatory pathologies that are currently endanger the lives of multifarious individuals worldwide.

AKNOWLEDGENENTS

Dr. Barabutis wish to acknowledge that his research is supported by **1)** Start - up funds (5RSPEC 300010 271008) to N.B from the College of Pharmacy, University of Louisiana Monroe, Monroe LA 71201 **2)** The Faculty Research Support Program from Dean’s Office (5CALHN-260615) to N.B from the College of Pharmacy, University of Louisiana Monroe, Monroe LA 71201 **3)** The Malcolm Feist Partners Across Campuses Seed Program (Fund 234054) to N.B (co-PI), Center for Cardiovascular Diseases and Sciences, Louisiana State University Health Shreveport, Shreveport, LA 71103 **4)** The Institutional Development Award (IDeA) from the National Institute of General Medical Sciences of the National Institutes of Health (5 P20 GM103424–15 and 3 P20 GM103424–15S1) to N.B.

REFERENCES

Barabutis N, & Catravas JD (2015). P53: The Wall Watcher. Medical & Surgical Urology. doi:10.4172/2168-9857.1000e112

Barabutis N, Dimitropoulou C, Birmpas C, Joshi A, Thangjam G, & Catravas JD (2015). p53 protects against LPS-induced lung endothelial barrier dysfunction. Am J Physiol Lung Cell Mol Physiol, 308(8), L776–787. doi:10.1152/ajplung.00334.2014 [PubMed: 25713322]

Barabutis N, Dimitropoulou C, Gregory B, & Catravas JD (2018). Wild-type p53 enhances endothelial barrier function by mediating RAC1 signalling and RhoA inhibition. J Cell Mol Med, 22(3), 1792–1804. doi:10.1111/jcmm.13460 [PubMed: 29363851]

Barabutis N, Handa V, Dimitropoulou C, Rafikov R, Snead C, Kumar S, … Catravas JD (2013). LPS induces pp60c-src-mediated tyrosine phosphorylation of Hsp90 in lung vascular endothelial cells and mouse lung. Am J Physiol Lung Cell Mol Physiol, 304(12), L883–893. doi:10.1152/ajplung.00419.2012 [PubMed: 23585225]

Barabutis N, & Schally AV (2008a). Antioxidant activity of growth hormone-releasing hormone antagonists in LNCaP human prostate cancer line. Proc Natl Acad Sci U S A, 105(51), 20470–20475. doi:10.1073/pnas.0811209106 [PubMed: 19075233]

Barabutis N, & Schally AV (2008b). Knocking down gene expression for growth hormone-releasing hormone inhibits proliferation of human cancer cell lines. Br J Cancer, 98(11), 1790–1796. doi:10.1038/sj.bjc.6604386 [PubMed: 18506184]

Barabutis N, & Schally AV (2010). Growth hormone-releasing hormone: extrapituitary effects in physiology and pathology. Cell Cycle, 9(20), 4110–4116. doi:10.4161/cc.9.20.13787 [PubMed: 20962577]

Barabutis N, Schally AV, & Siejka A (2018). P53, GHRH, inflammation and cancer. EBioMedicine. doi:10.1016/j.ebiom.2018.10.034

Barabutis N, Siejka A, & Schally AV (2011). Growth hormone releasing hormone induces the expression of nitric oxide synthase. J Cell Mol Med, 15(5), 1148–1155. doi:10.1111/j.1582-4934.2010.01096.x [PubMed: 20518847]

Barabutis N, Uddin MA, & Catravas JD (2018). Hsp90 inhibitors suppress P53 phosphorylation in LPS - induced endothelial inflammation. Cytokine. doi:10.1016/j.cyto.2018.10.020

Barabutis N, Verin A, & Catravas JD (2016). Regulation of pulmonary endothelial barrier function by kinases. Am J Physiol Lung Cell Mol Physiol, 311(5), L832–L845. doi:10.1152/ajplung.00233.2016 [PubMed: 27663990]

Bottazzi B, Riboli E, & Mantovani A (2018). Aging, inflammation and cancer. Semin Immunol. doi:10.1016/j.smim.2018.10.011

El-Hajjar L, Jalaleddine N, Shaito A, Zibara K, Kazan JM, El-Saghir J, & El-Sabban M (2018). Bevacizumab induces inflammation in MDA-MB-231 breast cancer cell line and in a mouse model. Cell Signal, 53, 400–412. doi:10.1016/j.cellsig.2018.11.007 [PubMed: 30445167]

Gupta SC, Kunnumakkara AB, Aggarwal S, & Aggarwal BB (2018). Inflammation, a Double-Edge Sword for Cancer and Other Age-Related Diseases. Front Immunol, 9, 2160. doi:10.3389/fimmu.2018.02160 [PubMed: 30319623]

Labuschagne CF, Zani F, & Vousden KH (2018). Control of metabolism by p53 - Cancer and beyond. Biochim Biophys Acta Rev Cancer, 1870(1), 32–42. doi:10.1016/j.bbcan.2018.06.001 [PubMed: 29883595]

Lane DP (1992). Cancer. p53, guardian of the genome. Nature, 358(6381), 15–16. doi:10.1038/358015a0 [PubMed: 1614522]

Levine AJ (2017a). The Evolution of Tumor Formation in Humans and Mice with Inherited Mutations in the p53 Gene. Curr Top Microbiol Immunol, 407, 205–221. doi:10.1007/82_2017_5 [PubMed: 28349284]

Levine AJ (2017b). The p53 protein plays a central role in the mechanism of action of epigentic drugs that alter the methylation of cytosine residues in DNA. Oncotarget, 8(5), 7228–7230. doi:10.18632/oncotarget.14805 [PubMed: 28129641]

Levine AJ (2018). Reviewing the future of the P53 field. Cell Death Differ, 25(1), 1–2. doi:10.1038/cdd.2017.181 [PubMed: 29227987]

Liu J, Zeng J, Wang X, Zheng M, & Luan Q (2018). P53 mediates lipopolysaccharide-induced inflammation in human gingival fibroblasts. J Periodontol, 89(9), 1142–1151. doi:10.1002/JPER.18-0026 [PubMed: 29964297]

Mendoza-Valdes A (2015). Introduction of Dr. Andrew V Schally. Asian J Androl, 17(6), 923–924. doi:10.4103/1008-682X.156852 [PubMed: 26112485]

Nanchal RS, & Truwit JD (2018). Recent advances in understanding and treating acute respiratory distress syndrome. F1000Res, 7. doi:10.12688/f1000research.15493.1

Popovics P, Cai R, Sha W, Rick FG, & Schally AV (2018). Growth hormone-releasing hormone antagonists reduce prostatic enlargement and inflammation in carrageenan-induced chronic prostatitis. Prostate, 78(13), 970–980. doi:10.1002/pros.23655 [PubMed: 29786867]

Sagiv A, Bar-Shai A, Levi N, Hatzav M, Zada L, Ovadya Y, … Krizhanovsky V (2018). p53 in Bronchial Club Cells Facilitates Chronic Lung Inflammation by Promoting Senescence. Cell Rep, 22(13), 3468–3479. doi:10.1016/j.celrep.2018.03.009 [PubMed: 29590616]

Thompson BT, Chambers RC, & Liu KD (2017). Acute Respiratory Distress Syndrome. N Engl J Med, 377(19), 1904–1905. doi:10.1056/NEJMc1711824

Tiwari B, Jones AE, & Abrams JM (2018). Transposons, p53 and Genome Security. Trends Genet, 34(11), 846–855. doi:10.1016/j.tig.2018.08.003 [PubMed: 30195581]

Wang P, Su H, Zhang L, Chen H, Hu X, Yang F, … Zhao Y (2018). Phosphatase wild-type p53-induced phosphatase 1 controls the development of TH9 cells and allergic airway inflammation. J Allergy Clin Immunol, 141(6), 2168–2181. doi:10.1016/j.jaci.2017.06.026 [PubMed: 28732646]

Xue H, & Li MX (2018). MicroRNA-150 protects against cigarette smoke-induced lung inflammation and airway epithelial cell apoptosis through repressing p53: MicroRNA-150 in CS-induced lung inflammation. Hum Exp Toxicol, 37(9), 920–928. doi:10.1177/0960327117741749 [PubMed: 29205062]