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Nektarios Barabutis
Old Dominion University

John D. Catravas
Old Dominion University, jcatrava@odu.edu

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P53: "The Wall Watcher"

Nektarios Barabutis[1]* and John D. Catravas[1,2]

[1]Frank Reidy Research Center for Bioelectrics, Old Dominion University, Norfolk, VA 23508, United States
[2]School of Medical Diagnostic and Translational Sciences, College of Health Sciences, Old Dominion University, Norfolk, Virginia, United States

The "guardian of the genome" was introduced in 1979 when p53 was recognized as the cellular partner of SV-40 large T antigen [1]. A plethora of independent studies revealed that this 53kDa protein is a transcription factor mostly mutated in human cancers which dictates cellular fate by signaling cell cycle arrest, apoptosis or senescence [2]. The intense cross - talking between inflammation and carcinogenesis, lead several groups to explore the anti-inflammatory role of p53 in malignancies. This effort revealed that the tumor suppressor activity of that molecule is associated with the induction of multiple anti-inflammatory responses both in cancerous and normal tissues [3]. The now well - established reciprocal negative regulation of p53 and NF-κB highlight the importance of p53 in the defense against inflammatory agents.

NF-κB-induced inflammatory cytokines reduce p53 transcriptional activity and agents that down regulate NF-κB cause p53 activation [4]. P53 is known to suppress the cyclooxygenase 2 gene and to antagonize pp60src-induced cell migration and proliferation in atherosclerosis [5,6]. P53 knockout mice are more susceptible to the LPS-induced acute lung injury, exhibit stronger responses to LPS stimulation, robust induction of pro-inflammatory cytokines and increased NF-κB DNA binding activity compared to the relevant wild type controls [7]. Mice with a p53 P72R mutation have an enhanced response to inflammatory challenges [8]. Bleomycin-induced pulmonary cell infiltration and disruption of alveolar architecture is increased in p53 null mice compared to wild type [9,10]. p53 null mice exposed to ionizing radiation exhibit a more rapid invasion of inflammatory cells and fibroblasts into the affected tissues than do wild type controls [11].

Hsp90 regulates the intracellular milieu by stabilizing and activating structural components, kinases and transcriptions factors which serve as important inflammatory mediators [12]. Although Hsp90 inhibitors were initially developed as antineoplastic drugs, an emerging body of evidence suggests that their anti-inflammatory activity enable them to have a beneficial role in the wider spectrum of human pathology [13-15]. We recently remonstrate that p53 is an Hsp90 client protein and that the anti-inflammatory and vascular barrier protective effects of Hsp90 inhibitors are due-at least in part- to p53 mediated actions [16].

Endothelial barrier dysfunction is a cause and consequence of inflammatory responses and is involved in the development of Acute Lung Injury (ALI) and the Acute Respiratory Distress Syndrome (ARDS) [17]. The barrier integrity in endothelial cells is regulated by the small GTPases Rac1 and RhoA, which orchestrate the barrier protective and disruptive elements of the endothelium [18]. They cycle between an inactive GDP- and an active GTP-bound state. This cycle is regulated by GTPase activating proteins (GAP), which increase the intrinsic rate of GTP hydrolysis and guanine nucleotide exchange factors (GEF), which push the GTPases into a GTP-bound state [19]. Rac1 and RhoA exert opposing effects on barrier function by inducing different patterns of cytoskeletal and cellular contact remodeling [20]. These modifications lead to either endothelial barrier protection, by strengthening the integrity of its key components, or to endothelial barrier dysfunction by opening endothelial cell junctions and promoting the formation of intracellular gaps [21]. Conversely, activation of RhoA by inflammatory mediators, including LPS, activates ROCK1/2 which in turn induces the phosphorylation of myosin light chain kinase II [22]. These effects result in actomyosin contraction, actin stress fiber formation and barrier integrity disruption [23].

The robust p53-induced anti-inflammatory responses are partially mediated by the regulation of the Rho GTPases; namely the restriction of the Ras-induced RhoA stimulation and the resulting suppression of MLCII phosphorylation [24]. RhoA activity is enhanced in p53-/- cells. P53 negatively regulates the expression of RhoA, ROCK1 and ROCK2 [25]. The latter is exerted via transcriptional regulation of Notch1, which negatively regulates ROCK expression [26]. We have recently demonstrated both in vivo and in vitro that Hsp90 inhibitors stabilize p53 which in turn protects against LPS-induced endothelial barrier dysfunction by disrupting the RhoA/MLCII inflammatory pathway [16]. Thus, p53 appears to regulate endothelial cellular function by orchestrating protective responses towards the suppression of host-directed inflammation. Future studies will likely enlighten the expanding p53 universe by elucidating the exact role of the cellular Wall Watcher on the maintenance of the vascular integrity.

References

1. Lane DP (1992) Cancer. p53, guardian of the genome. Nature 358: 15-6.
2. Lane D, Levine A (2010) p53 Research: the past thirty years and the next thirty years. Cold Spring Harb Perspect Biol 2: a000893.
3. Gudkov AV, Gurova KV, Komarova EA (2011) Inflammation and p53: A Tale of Two Stresses. Genes Cancer 2: 503-516.
4. Pal S, Bhattacharjee A, Ali A, Mandal NC, Mandal SC, et al. (2014) Chronic inflammation and cancer: potential chemoprevention through nuclear factor kappa B and p53 mutual antagonism. J Inflamm (Lond) 11: 23.
5. Subbaramaiah K, Altorki N, Chung WJ, Mestre JR, et al. (1999) Sampat A,Inhibition of cyclooxygenase-2 gene expression by p53. J Biol Chem 274: 10911-10915.
6. Mukhopadhyay UK, Eves R, Jia L, Mooney P, Mak AS (2009) p53 suppresses Src-induced podosome and rosette formation and cellular invasiveness through the upregulation of caldesmon. Mol Cell Biol 29: 3088-3098.
7. Liu G, Park YJ, Tsuruta Y, Lorne E, Abraham E (2009) p53 Attenuates lipopolysaccharide-induced NF-kappaB activation and acute lung injury. J Immunol 182: 5063-5071.
8. Frank AK, Leu JI, Zhou Y, Devarajan K, Nedelko T, et al. (2011) The codon 72 polymorphism of p53 regulates interaction with NF-{kappa}B and transactivation of genes involved in immunity and inflammation. Mol Cell Biol 31: 1201-1213.
9. Ghosh S, Mendoza T, Ortiz LA, Hoyle GW, Fermin CD, (2002) Bleomycin sensitivity of mice expressing dominant-negative p53 in the lung epithelium. Am J Respir Crit Care Med 166: 890-897.
10. Davis DW, Weidner DA, Holian A, McConkey DJ (2000) Nitric oxide-dependent activation of p53 suppresses bleomycin-induced apoptosis in the lung. J Exp Med 192: 857-869.

***Corresponding author:** Nektarios Barabutis, Frank Reidy Research Center for Bioelectrics, Old Dominion University, Norfolk, VA 23508, United States, Tel: 706-294-9169; E-mail: nbarabut@odu.edu

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11. Komarova EA, Kondratov RV, Wang K, Christov K, Golovkina TV, et al. (2004) Dual effect of p53 on radiation sensitivity in vivo: p53 promotes hematopoietic injury, but protects from gastro-intestinal syndrome in mice. Oncogene 23: 3265-3271.

12. Rice JW, Veal JM, Fadden RP, Barabasz AF, Partridge JM, et al. (2008) Small molecule inhibitors of Hsp90 potently affect inflammatory disease pathways and exhibit activity in models of rheumatoid arthritis. Arthritis Rheum 58: 3765-3775.

13. Barabutis N, Handa V, Dimitropoulou C, Rafikov R, Snead C, et al. (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: L883-893.

14. Chatterjee A, Snead C, Yetik-Anacak G, Antonova G, Zeng J, et al. (2008) Heat shock protein 90 inhibitors attenuate LPS-induced endothelial hyperpermeability. Am J Physiol Lung Cell Mol Physiol 294: L755-763.

15. Barabutis N, Catravas JD (2013) Anti-Inflammatory Activity of Hsp90 Inhibitors in the Human Vasculature. Med Surg Urol 2:e104.

16. Barabutis N, Dimitropoulou C, Birmpas C, Joshi A, Thangjam G, et al. (2015) p53 protects against LPS-induced lung endothelial barrier dysfunction. Am J Physiol Lung Cell Mol Physiol 308: L776-787.

17. Matthay MA, Zimmerman GA (2005) Acute lung injury and the acute respiratory distress syndrome: four decades of inquiry into pathogenesis and rational management. Am J Respir Cell Mol Biol 33: 319-327.

18. Birukov KG (2009) Small GTPases in mechanosensitive regulation of endothelial barrier. Microvasc Res 77: 46-52.

19. Hanna S, El-Sibai M (2013) Signaling networks of Rho GTPases in cell motility. Cell Signal 25: 1955-1961.

20. Lamouille S, Xu J, Derynck R (2014) Derynck, Molecular mechanisms of epithelial-mesenchymal transition. Nat Rev Mol Cell Biol 15: 178-196.

21. Dejana E, Orsenigo F, Lampugnani MG (2008) The role of adherens junctions and VE-cadherin in the control of vascular permeability. J Cell Sci 121: 2115-2122.

22. Liao JK, Seto M, Noma K (2007) Rho kinase (ROCK) inhibitors. J Cardiovasc Pharmacol 50: 17-24.

23. Arce FT, Whitlock JL, Birukova AA, Birukov KG, Arnsdorf MF, et al. (2008) Regulation of the micromechanical properties of pulmonary endothelium by S1P and thrombin: role of cortactin. Biophys J 95: 886-894.

24. Croft DR, Olson MF (2011) Transcriptional regulation of Rho GTPase signaling. Transcription 2: 211-215.

25. Gadea G, de Toledo M, Anguille C, Roux P (2007) Loss of p53 promotes RhoA-ROCK-dependent cell migration and invasion in 3D matrices. J Cell Biol 178: 23-30.

26. Lefort K, Mandinova A, Ostano P, Kolev V, Calpini V, et al. (2007) Notch1 is a p53 target gene involved in human keratinocyte tumor suppression through negative regulation of ROCK1/2 and MRCKalpha kinases. Genes Dev 21: 562-577.

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