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Forum Editorial

APE1/Ref-1: Versatility in Progress

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Abstract

Apurinic/apyrimidinic endonuclease1/redox factor-1 (APE1/Ref-1) is a multifunctional protein involved in base excision DNA repair and in transcriptional regulation of gene expression. Over the past decade and a half, knowledge of the biological functions, interactions, mechanisms of action, and regulation of the protein APE1/Ref-1 has grown exponentially. The multifunctional nature of APE1/Ref-1 is uncovering and has been extensively studied in the cellular response against oxidative stress. Recent evidence shows a biological role of APE1/Ref-1 can be modulated by the different post-translational modification. Because of APE1/Ref-1 importance to genomic stability and cell survival, APE1/Ref-1 is focused as the leading therapeutic target molecule for the oxidative stress condition or pathologic conditions such as cancer. This forum, dedicated to APE1/Ref-1, provides ample testimony that even though we have learned a great deal about APE1/Ref-1 over the past 15-plus years, our knowledge still constitutes the tip of the iceberg when it comes to understanding this versatile protein. *Antioxid. Redox Signal*. 11, 571–573.

First identified as a mammalian apurinic/apyrimidinic endonuclease, and termed APE1 and human AP1 (HAP1) (5, 13), it was then quickly found to possess other biological functions, including its ability to reductively activate redox-sensitive transcription factors (15), and negative gene regulation by extracellular calcium (12). Since being first recognized as a critical "caretaker" of the genome, the momentum to identify novel functions and mechanisms of APE1/Ref-1 has only grown.

Inflammation and APE1/Ref-1 are no strangers. APE1/Ref-1 plays a complex role in the activation of nuclear factor-kappa B (NF-κB), a key transcription factor involved in inflammatory and immune signaling. On the one hand, APE1/Ref-1 reductively activates NF-κB by stimulating its DNA-binding activity in the nucleus (16). On the other hand, cytoplasmic APE1/Ref-1 may antagonize NF-κB activation by suppressing nuclear translocation of NF-κB (1), a key step required in its activation. In this forum, a report by Eun-Kyeong Jo and colleagues adds to this Jekyl and Hyde role of APE1/Ref-1 in inflammatory signaling (20). The authors demonstrate that APE1/Ref-1 also has a complex relationship to high-mobility group box 1 (HMGB1), a protein secreted by immune cells in response to inflammatory stimuli, and one that itself functions as a pro-inflammatory cytokine in sepsis and autoimmune diseases. The work by Jo and coworkers suggests that, not unlike its part in NF-κB activation, APE1/Ref-1 can both promote and suppress inflammatory signaling induced by HMGB1, and this dual function may be a consequence of the subcellular localization, and the HMGB1-induced change in this localization, of APE1/Ref-1 in immune cells. Alas, APE1/Ref-1 has evaded another effort to pigeonhole it into a pro- or anti-inflammatory factor.

Post-translational regulation of APE1/Ref-1 function is a fertile area for investigation. Phosphorylation of APE1/Ref-1 by several different kinases has been shown to affect both its DNA repair and reducing properties (6, 9, 17). Equally interesting is the proposition that APE1/Ref-1 is acetylated and that this modification impacts on, or is important for, its function(s). A study by Mitra and colleagues demonstrated that APE1/Ref-1 is acetylated in cells that have evolved to sense a decrease in extracellular calcium, and this acetylation is necessary for the repression of parathyroid hormone (PTH) secretion by APE1/Ref-1 (3). How acetylated APE1/Ref-1 functions in this manner is not known. There are now suggestions that acetylation of APE1/Ref-1 may modulate its ability to interact with other proteins such as

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the Y-box-binding protein YB-1, thereby regulating the transcription of its target genes such as multidrug resistance 1 (MDR1) (4). Such findings add a new and exciting dimension to the known transcriptional regulatory function of APE1/Ref-1: regulation of transcription through redox-independent mechanisms. They also raise the intriguing possibility that acetylation of APE1/Ref-1 may serve to modulate other post-translational modifications that target lysine residues such as sumoylation. Indeed, preliminary evidence does suggest that APE1/Ref-1 may be sumoylated (14). However, whether and how sumoylation affects APE1/Ref-1 function, expression, or localization remains an open question.

APE1/Ref-1 has received growing attention for its role in cardiovascular physiology and pathophysiology. Among others, APE1/Ref-1 suppresses myocardial ischemia–reperfusion injury (7) and vascular inflammation (11), and promotes endothelium-dependent vascular relaxation (10). Das and colleagues now report that APE1/Ref-1 also plays a part in maintaining adult cardiac stem cells in an undifferentiated state (8). Recognizing the potential of cardiac stem cells in regenerative cardiovascular medicine, this finding is likely to spur new interest in manipulating APE1/Ref-1 as means of enhancing stem cell survival and function.

Perhaps the most exciting and tangible gain to be derived from our greater understanding of the functions and mechanisms of APE1/Ref-1 is in the domain of cancer therapeutics. Increased levels of APE1/Ref-1 in tumors have been associated greater resistance to chemotherapy and carry a poorer prognosis. It is believed that the DNA repair activity of APE1/Ref-1 is responsible for the chemoresistance of many cancer cells. Thus, targeting this activity in tumors that have high expression of APE1/Ref-1 could theoretically sensitize these tumors to killing by chemotherapeutic agents. In this forum, Kelley and colleagues (2) report high throughput screening assays and identification of lead compounds that selectively inhibit the endonuclease activity of APE1/Ref-1. Such compounds can be potentially developed into adjuvants for cancer chemotherapies. In a similar vein, Meyskens and co-workers (19) raise the exciting possibility that resveratrol, and resveratrol analogues, that have been shown to inhibit the endonuclease activity of APE1/Ref-1 (18), may provide a starting point for the development of more effective chemotherapies for melanoma, a devastating cancer that has high expression of APE1/Ref-1 (18).

In summary, an explosion of studies since the early 1990s has added greatly to our understanding of the protein APE1/Ref-1. Many of these studies underscore the multiple functions, and the complex mechanisms and regulation of APE1/Ref-1. However, judging from the past, it is likely that our understanding is not yet complete. Future studies will almost certainly yield new secrets about the versatile nature of this protein.

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