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# A Novel Oxidative Stress-Responsive Apoptosis Inducing Protein (ORAIP) may have Possible Effects on Immune Disorders

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**Abstract**

We previously identified a novel apoptosis inducing humoral factor in the conditioned medium of hypoxic/reoxygenated cardiac myocytes. Myocardial ischemia/reperfusion markedly increased plasma ORAIP levels and myocardial ischemia/reperfusion injury was clearly suppressed by neutralizing anti-ORAIP antibodies *in vivo*. We named this novel post-translationally modified secreted-form of eukaryotic translation initiation factor 5A, as Oxidative Stress-Responsive Apoptosis Inducing Protein (ORAIP). Evidence has accumulated that ORAIP may be a common and the dominant apoptosis-inducer among various cell types in response to various types of oxidative stress involved in a wide spectrum of acute and chronic disorders. We found infiltrating immune cells strongly expressed ORAIP in the tissues with myocarditis, aortitis, and atherosclerosis, suggesting that ORAIP-mediated apoptotic signalling may play a role in the pathogenesis involved. Further investigation is needed to confirm whether ORAIP can be a sensitive biomarker and a therapeutic target for the cell injury involved in immune disorders.

**Keywords:** Eukaryotic translation initiation factor 5A (eIF5A); Ischemia/reperfusion (I/R) injury; Oxidative stress; Oxidative Stress-Responsive Apoptosis Inducing Protein (ORAIP)

## Description

Oxidative stress is known to play a critical role in the pathogenesis of various disorders, especially Ischemia/Reperfusion (I/R) injury, ultraviolet/radiation injury, as well as chronic diseases such as diabetes mellitus, atherosclerosis, dyslipidemia, chronic renal disease, and immune diseases. Although Reactive Oxygen Species (ROS) have been proposed as the key mediator of oxidative stress-induced cell injury for long periods, antioxidant therapies (such as free radical scavengers, vitamins) have failed in improving cardiovascular diseases in clinical trials, raising a possibility that some unknown mechanisms other than ROS may be involved in oxidative stress-induced cell injury.

We previously reported a novel apoptosis-inducing humoral factor in a conditioned medium from cardiac myocytes subjected to hypoxia/reoxygenation [1]. We found that this novel secreted form of eukaryotic translation initiation factor 5A (eIF5A) is sulfated at the 69th tyrosine residue and contains more hypusinated isoform than conventional cytosolic form of eIF5A, and is rapidly secreted from cardiac myocytes in response to hypoxia/reoxygenation, then, induces apoptosis of the cells by acting as a pro-apoptotic ligand in an autocrine fashion (Figure 1).

We referred to this novel tyrosine-sulfated secreted form of eIF5A, as Oxidative Stress-Responsive Apoptosis Inducing Protein (ORAIP) [1]. We found that myocardial and cerebral I/R (but not ischemia alone) rapidly and markedly increased plasma or cerebrospinal fluid levels of ORAIP and *in vivo* anti-ORAIP neutralizing monoclonal antibody treatment significantly reduced I/R injury [1,2]. We also found that the plasma or tissue levels of ORAIP were significantly elevated in patients with chronic renal disease, dyslipidemia, diabetes mellitus, diabetic retinopathy, and heart failure, in which oxidative stress plays a critical role in the pathogenesis involved [3-6]. Plasma ORAIP concentrations were also significantly increased in response to physicochemical stresses such as hypoxia/reoxygenation, ultraviolet light, ionizing radiation, heat shock, and so on [7]. It seems that secretion of ORAIP is specific to various kinds of oxidative stresses in a variety of cell types especially cardiac and skeletal myocytes, neurons, and cancer cells, those need a lot of oxygen for their activities and hence susceptible to oxidative stress-induced apoptosis mainly mediated by ORAIP. These results strongly suggested that ORAIP may be a specific biomarker and a critical therapeutic target for the oxidative stress-induced cell injury involved in a wide spectrum of acute and chronic disorders. Researches on ORAIP are accumulating evidence to support that ORAIP may be a common and the dominant apoptosis-inducing ligand induced in response to the oxidative stresses. Recently, we have identified a single cell-surface receptor for ORAIP (ORAIP-receptor; unpublished data), through which ORAIP transduces the apoptotic signal intracellularly.

For immune-mediated inflammatory diseases, we found that infiltrating immune cells strongly expressed ORAIP in the tissues with acute myocarditis, aortitis, and atherosclerosis, and some parts of cardiac myocytes and arterial smooth muscle cells expressed ORAIP-

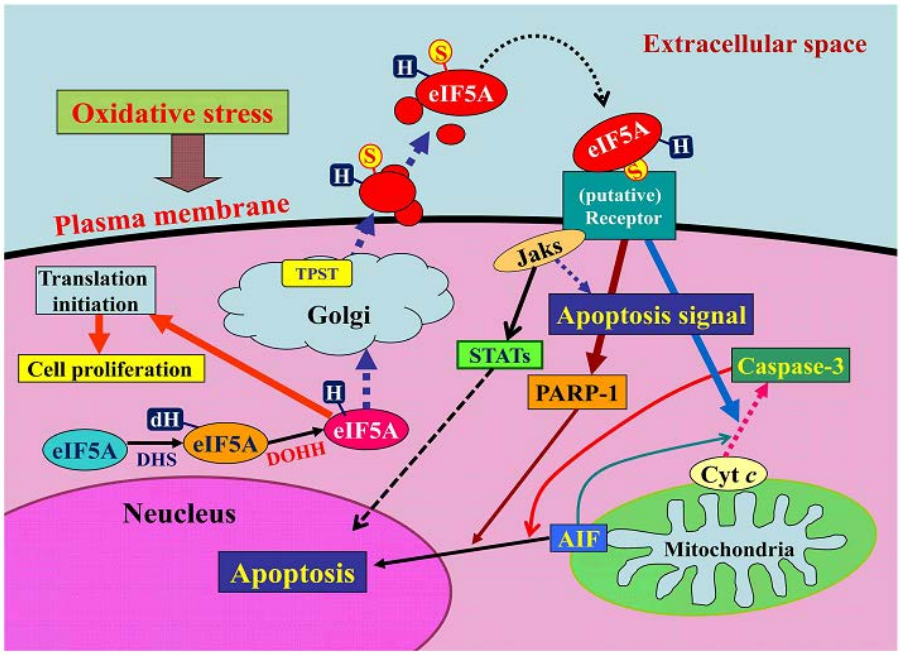


**Figure 1:** A model for the mechanism by which oxidative stress induces apoptosis *via* the autocrine secretion of eIF5A (ORAIP). **Abbreviations:** AIF: Apoptosis-Inducing Factor; Cyt-c: Cytochrome C; DH: Deoxyhypusine; DHS: deoxyhypusine Synthase; DOHH: Deoxyhypusine Hydroxylase; H: Hypusine; Jaks: Janus kinases; S: Sulfated; PARP-1: Poly (ADP-Ribose) Polymerase-1; STATs: Signal Transducers and Activators of Transcriptions; TPST: Tyrosylprotein Sulfotransferase [1].

receptor (unpublished observation). This suggests that infiltrating immune cells may induce apoptosis in myocardial and arterial cells through ORAIP/ORAIP-receptor pathway as well as directly injure them with cytotoxic factors such as perforin. It has been thought that the plaque rupture often associates with thrombosis and plays the leading role in acute coronary syndrome and cerebral infarction. However, the precise mechanism of plaque vulnerability leading to rupture has been unclear. We also found that oxidized low-density lipoprotein and ORAIP were co-expressed in the atherosclerotic plaque, may be due to the oxidative stress at the site of plaque formation, in which a part of smooth muscle cells expressing ORAIP underwent apoptosis. This suggests that ORAIP-induced apoptosis in smooth muscle cells may play a role in inducing plaque vulnerability. Along with these findings, further investigation on a role of ORAIP/ORAIP-receptor pathway in various disorders including immune diseases will shed light on the unknown mechanisms in the pathogenesis involved.

## Discussion and Conclusion

Since we discovered a novel secreted form of eIF5A to be the Oxidative Stress-Responsive Apoptosis Inducing Protein (ORAIP), we found that plasma levels of ORAIP were clearly elevated in a wide range of acute and chronic disorders, in which ORAIP plays a critical role in the pathogenesis involved. Because we found ORAIP was involved in the immune response in some cardiovascular inflammatory diseases, further investigation is needed to warrant anti-ORAIP therapy for the cell injury involved in immune disorders including mucosal diseases.

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