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Increased Cardioprotective Capacity of Cardiomyocytes during Hypoxia: A Possible Role of Cap Independent Translation

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Abstract: **Heart is the sensitive organ to hypoxia and in response to low oxygen availability numerous adaptive responses are initiated at the molecular, cellular and organ level. Cardiomyocytes increase their cardioprotective capacity in response to hypoxic conditions to survive the stress conditions. There are different possibilities, like increased transcriptions or translation which will account for the increased cardioprotective capacity of cardiomyocytes under hypoxic conditions. However, none of these account fully with the observed increase in the cardioprotective activity of cardiomyocytes. Moreover, it is well known that during hypoxia the cap dependent protein translation is decreased, but still expression levels of few cardioprotective mRNAs are enhanced. Cap-independent translation, mediated by Internal Ribosome Entry Sites (IRES) is an alternative strategy used by cells to maintain the translation rate of some mRNAs under stress conditions, like hypoxia. Thus we hypothesize that cap-independent translation may play a critical role in enhancing the cardioprotective role of cardiomyocytes under hypoxic conditions.**

Keywords: **Hypoxia, cardioprotection, Internal Ribosome Entry Sites, 5′ untranslated region.**

1. INTRODUCTION

A constant supply of oxygen is indispensable for cardiac viability and function [1]. Hypoxia is the deficiency either in the delivery or the utilization of oxygen at the cellular level [2], which can alter various physiological functions at cellular level. In humans, the hypoxic conditions occur during various pathophysiological conditions, like stroke, myocardial ischemia, tumorous growth, etc [3]. Heart is considered to be the sensitive organ towards hypoxia and in response to hypoxia numerous adaptive responses at the molecular and cellular as well as at the whole organ level are initiated [4]. The way by which cardiomyocytes respond to hypoxia would significantly affect the response of the heart to hypoxia and the extent of heart injury in pathological conditions involving hypoxia [5]. One of the ways the cardiomyocytes respond to hypoxia is to increase the cardioprotective capacity by regulating its cardioprotective proteins. Molecular studies carried out in this regard have mainly focused on the post-translational modification of cardioprotective proteins in response to hypoxia. Thus, it is important to elucidate other molecular events underlying the response of cardiomyocytes to hypoxia.

Cardiomyocytes are highly adapted to with stand hypoxic insults, indicating evolution of cardioprotective mechanisms. There are number of well defined responses that many cells have to chronic hypoxia. These includes down regulation of mechanisms that consume ATP such as inhibition of protein synthesis, protein breakdown and gluconeogenesis etc [6]. It has been demonstrated that cardiomyocytic ATP demand decreases upon deprivation of oxygen and glucose [2]. Moreover, cardiomyocytes also down regulate global protein synthesis as evidenced by disruption of polyribosomes [7]. It has also been found that cardiomyocytes respond to hypoxia by increase their cardioprotective capacity. This increased ability of cardioprotection is due to coordinated up regulation of cardioprotective proteins like Heat shock protein 70 (HSP70) [8], Heme oxygenase (HO-1) [9], Sulphonylurea receptor 2A (SUR2A) [10], Nitric Oxide synthase (NOS) [11]

etc. What accounts for the hypoxia induced up regulation of cardioprotective proteins is not fully understood. One possibility is due to increased availability of mRNA through enhanced transcription such as that mediated by Hypoxia Inducible Factor-1 (HIF-1) or by post transcriptional changes resulting in enhanced stability of mRNA. However, none of these account fully with the observed increase in the cardioprotective capacity during hypoxia. However, cap-independent translation, mediated by Internal Ribosome Entry Sites (IRES) is an alternative strategy used by cells to maintain the translation rate of some mRNAs under stress conditions, like hypoxia [12].

Elucidating the molecular events responsible for the increased cardioprotective capacity of cardiomyocytes will help us to better understand the role of these cells in human heart during hypoxic condition. Sequence analysis of the different cardioprotective mRNAs like HSP70, SUR2A and NOS has revealed the presence of long 5′ untranslated region (5′ UTR) regions and therefore indicates chances of the cap-independent translation. Moreover, many polypyrimidine tract binding protein (PTB) consensus sequence elements CCUC in the context of long stretches of polypyrimidine tracts were found in the 5-UTRs of various cardioprotective proteins.

Regulation at the level of translation of mRNA is one of the mechanisms of control of gene expression in eukaryotes. Translation of most eukaryotic mRNAs involves interaction of the mRNA 5'- m7GpppN cap with the eIF4E (eukaryotic initiation factor 4E) subunit of the eIF4F translation initiation complex [13]. A broad range of cellular stresses, including hypoxia lead to the inhibition of cap-dependent translation [14]. An alternative mode of translation initiation that does not require eIF4E and the 5'-cap involves recruitment of the translation initiation complex by an IRES elements present in the 5'-UTR of these mRNAs. It is widely supposed that cap-independent internal initiation may maintain efficient translation of particular cellular mRNAs under a variety of stresses and other special conditions when cap-dependent protein synthesis is impaired [15]. IRESs were shown to be active in stress situations when cap-dependent translation is repressed, including hypoxia [12] [16]. This led to the current hypothesis that IRES-mediated translation of certain mRNAs represents a regulatory mechanism that helps the cell to cope with transient stress. The molecular mechanism of IRES-mediated translation is obscure, but it is clear that there is no single universal mechanism used by all IRES elements. Most other IRESs depend on canonical translation initiation factors and non-canonical IRES transacting factors (ITAFs) for efficient initiation of translation. One such ITAF is polypyrimidine tract binding protein (PTB) which binds to pyrimidine rich regions within different IRES sequences modulates the activity of the IRESs. Interestingly, binding of PTB to various IRES elements has been found to be enhanced with hypoxia [17].

2. CONCLUSION

Under conditions of hypoxia, the ability of cardiomyocytes to up regulate the expression of cardioprotectve genes might be the deciding factor in determining whether cells survive. Molecular mechanism responsible for the increased cardioprotectve capacity of cardiomyocytes during hypoxia will help in understanding the cardioprotective role of cardiomyocytes and devising therapeutic strategy to enhance this role during heart hypoxia, thus protecting heart from the irreversible damage.

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