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Invited Review

Modulation of heat shock proteins by statins

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ABSTRACT

Heat shock proteins (HSP or stress proteins) are intracellular molecules that participate in physiological cell metabolism and growth, although they are known to be involved in many stress conditions. Statins inhibit the action of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA), which is important in the synthesis of cholesterol and essential isoprenoid intermediates, thereby lowering circulating low-density lipoprotein cholesterol (LDL), a major risk factor for cardiovascular disease (CVD). This review provides new insights into the mechanisms of action of statins in the regulation of HSPs. A better understanding of this involvement can help in development of new and more effective treatment strategies for CVD.

1. Introduction

The Italian scientist, Ferruccio Ritossa, and his co-workers discovered the heat shock proteins (HSPs) in 1962, when they noted that temperature shock caused the induction of odd puffing patterns and an unusual profile of gene expression in the polytene chromosomes of salivary gland cells of Drosophila larvae [1]. However, the products of these genes were first identified in 1974 and called HSPs [2]. The synthesis of HSP molecules is a universal phenomenon and they can be induced in both eukaryotic and prokaryotic species. Mammalian cells constitutively expressed HSP (as approximately 5–10% of the total protein content under healthy growth conditions), but insults such as oxidative stress, toxic compounds, viral infection, and ischemia-reperfusion damage can also lead to incremental increases in their intracellular concentrations that induce protein unfolding, misfolding or aggregation, and a flux of newly-synthesized non-native proteins. HSPs constitute a large family of proteins and, based on their molecular mass, they are classified into numerous families including: HSP 27, HSP40, HSP 47, HSP 60, HSP70, HSP90, HSP100 and HSP110 [3–5]. In the present review, we highlight the role of statin on lowering LDL, and discuss how it can regulate HSPs. For a summary of the localization and functions of HSPs see Table 1.

2. Role of statins

Statins are one of the most frequently prescribed groups of drugs worldwide [6–8]. Statins inhibit HMG-CoA reductase, the rate limiting step of cholesterol synthesis [9]. It has been shown that statin therapy lowers LDL-C levels by 20–50%, as well as lowering triglycerides by 10–20% and increasing serum high density lipoprotein cholesterol (HDL-C) levels by 5–10% [10–12]. Statins are the most commonly prescribed class of drugs for treatment of hypercholesterolemia and in patients with, or at risk for, CVD. Using statin therapy decreases the risk of cardiovascular morbidity and mortality [13–15]. Over 25% of adults 65 and older take a statin on a long-term basis, both for primary and secondary prevention of CVD [13].

3. Pleiotropic effects of statins

A number of studies indicate that some of the cholesterol-independent, or pleiotropic, effects of statins include improving or restoring endothelial function, enhancing the stability of atherosclerotic plaques, normalization of sympathetic outflow, antiproliferative and immunomodulatory effects, reducing oxidative stress and inflammation

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Table 1
Heat shock protein families and their intracellular location and function.

Heat shock protein	Intracellular localization	Known functions	References
HSP27	Cytosol	Promoting cell survival, Cytoprotection, Cell differentiation and embryogenesis	[109,110,111,112]
HSP40	Cytosol	HSP70 and HSP40 cooperate in renaturation of heat-denatured proteins in intact mammalian cells. Repair denatured proteins, together with HSP70/Hsc70	[113,114]
HSP47	ER	Synthesis/assembly of several collagens, a member of serpin (serine protease inhibitor) superfamily	[115]
HSP60	Mitochondria	Cytoprotection; macrophage activator possibly through Toll like receptors	[116]
HSP70	Cytosol/ Nucleus	Cytoprotection and antiapoptotic, HSP70-2 involved in spermatogenesis	[117,118]
HSP90α	Cytosol	Protein folding, peptide chaperone, cytoprotection, intracellular signaling (e.g., steroid receptor), cell-cycle control and buffering of harmful mutations	[119]
HSP90β	Cytosol	Main cytosol chaperone; protein folding; cytoprotection; intracellular signaling (e.g., steroid receptor); cell-cycle control; and buffering of harmful mutations	[118] [120]
α-A crystallin	Mainly in the vertebrate eye lens; trace amount in other tissues	Structural protein of eye lens	[121]
α-β crystallin	Cytosol	Antiapoptotic, thermoprotection	[118]
Calnexin	ER	Folding of glycoproteins	[118]
Calreticulin	ER, Cell surface	Folding of glycoproteins; facilitates peptide loading to the class I molecule of the major histocompatibility complex	[122]
Gp96 (otherwise known as grp94)	ER, Cell surface	Regulation of protein homeostasis in the ER; involved in the activation of dendritic cells and chaperoning of antigenic peptides in the process of antigen presentation	[123] [124]
Grp170	ER	Involved in peptide transport in the ER	[125]
Grp78	ER	Protein (e.g., immunoglobulin) folding	[118]
Hsc70	Cytosol/ Nucleus	Protein folding, clathrin uncoating, peptide binding	[118]

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