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Review Article

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Physiological Relevance of the TLQP-21 and HSPA8 Interaction: A Review

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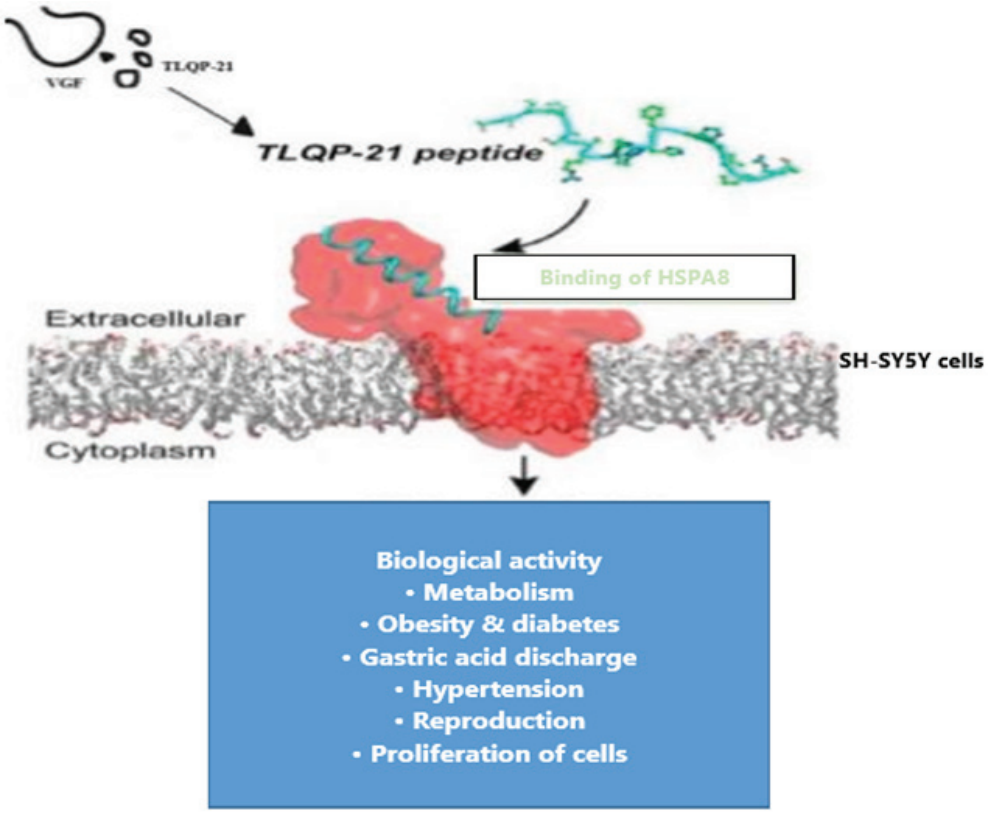
Abstract

By means of affinity chromatography and mass spectrometry-based protein identification, the heat shock cognate 71 kDa protein A8 (HSPA8) has been identified as a receptor of human TLQP-21. Cross-linking and FACS studies also established the binding of TLQP-21 to membrane associated HSPA8 in live SH-SY5Y cells. Additionally, TLQP-21 was found, as per in silico molecular modeling studies, to fit (docked) very well into the peptide binding pocket of HSPA8. So, it is expected that there would be physiological relevance between TLQP-21 and HSPA8 interaction. The aim of the review is to show the physiological relevance of the TLQP-21 and HSPA8 interaction. The physiological relevance of the TLQP-21 and HSPA8 interaction was evident in energy homeostasis, obesity, diabetes, reproduction, gastric acid secretion and hypertension. The major task moving forward is to elucidate the signaling pathways of the physiological relevance of the ligand TLQP-21 and its receptor HSPA8 to discover a new avenue for remedies where TLQP-21 has been found to have relation with human diseases.

Key words: *TLQP-21; HSPA8; Physiological relevance; HSP family.*

Abbreviations: CaM: calmodulin; FACS: Fluorescence-activated cell sorting; HSPA8: Heat shock cognate protein A8; HSPs: Heat shock proteins; HSP1A: Heat shock protein 1A; HSP70: Heat shock protein 70 (family); HPG: Hypothalamic-pituitary-gonadal; kDa: Kilo Dalton; Da: Dalton; MS: Mass spectrometry; SRY: Sex determining region on the Y chromosome; SH-SY5Y: A thrice cloned (SK-N-SH → SH-SY → SH-SY5 → SH-SY5Y) subline of the neuroblastoma cell line; TLQP-21: The first four amino acids, in short TLQP (Thr-Leu-Gln-Pro) generalizes the nomenclature of the peptide by its length; T2DM: Type 2 diabetes mellitus; VGF: Non acronymic, a neurotrophin; WAT: White adipose tissue



Graphical abstract: physiological relevance of the TLQP-21 and HSPA8 interaction (Modified from Cero et al., 2014).

Introduction

Out of several bioactive peptides derived from VGF, TLQP-21 is of great importance because of its many physiological roles. TLQP 21 plays a key role in energy expenditure (Possenti et al., 2012; Jethwa et al., 2007; Bartolomucci et al., 2006), metabolic functions (Bartolomucci et al., 2008), lipolysis (Possenti et al., 2012), glucose-stimulated insulin secretion (GSIS) (Stephens et al., 2012), nociception (Fairbanks et al., 2014; Chen et al., 2013; Rizzi et al., 2008), blood pressure/hypertension regulation (Fargali et al., 2014), gastric contractility (Severini et al., 2009; Bartolomucci et al., 2008), regulation of gastric acid secretion (Sibilia et al., 2012; Sibilia et al., 2010a; 2010b) reproduction (Aguilar et al., 2013; Pinilla et al., 2011), stress (Razzoli et al., 2012, Bartolomucci et al., 2011), neuroprotective agent (Severini et al., 2008), anorexia (Bartolomucci et al., 2006; Jethwa et al., 2007).

TLQP-21 (human) is of molecular weight 2490.88 Da. The peptide sequence is –

TLQPPSALRRRHYHHALPPSR

Thr - Leu - Gln - Pro - Pro - Ser - Ala - Leu - Arg - Arg - Arg - His - Tyr His - His - Ala - Leu - Pro - Pro - Ser – Arg

HSPA8

HSPA8 (Heat shock cognate protein A8, 71 kDa), a constitutively expressed protein, is a fascinating member of the HSP70 (Heat shock protein) family. It is also referred to as stress inducible protein.

While HSPA8 is usually localized within the cytoplasm and nucleus, where it carries out a variety of functions that are discussed below, it can also be found in a membrane-bound manner on cell surfaces, particularly in cancer cells, undifferentiated human embryonic stem cells, virus transformed B cells (Liao and Tang, 2014; Mambula et al., 2006; Kettner et al., 2007; Powers et al., 2008).

While HSPA8 is involved in housekeeping chaperoning functions (He M et al., 2010; Pfaffenbach et al., 2010; Daugaard et al., 2007; Powers et al., 2008), that is not its only role: additionally, it carries out biological functions relevant to immunity, antigenicity, hematopoiesis, autophagy (Stricher et al., 2013), vesicular trafficking, exocytosis, endocytosis and participates in multiple cellular signalling pathways (Meimaridou et al., 2009).

The HSP family of proteins

HSPs, the protein family to which HSPA8 belongs, are ubiquitously distributed and highly expressed in tissues (Hantschel et al., 2000). There are evidences of plasma membrane localization of cytoplasmin HSPs ranging from 70 to 90 KDa, though some of them term it as 'unusual plasma membrane localization of cytoplasmin HSPs'(Altmeyer et al., 1996; Ferrarini et al., 1992; Piselli et al., 1995; Tamura , et al., 1993). In fact, HSPs are contained intracellularly but they are translocated into the plasma membrane and released into the extracellular environment especially after various pathological conditions (Campisi, 2003; Singh-Jasuja, 2001; Srivastava, 2002, Vega et al., 2008). It is now well established that the HSPs act in various intracellular compartments (Buchner, 1996; Frydman and Hohfeld, 1997; Hartl, 1996; Hightower, et al., 1994; Melnick and Argon, 1995), although there are evidences suggesting the function of certain HSPs after being expressed on the cell surface (Kaur, et al., 1993, Takashima, et al., 1996; Tamura, et al., 1993; Tsuboi, et al., 1994). HSPs interact with the proteins in unfolded, misfolded or aggregated states but do not react with the folded counterparts. However, they can interact with a limited set of native proteins (Mayer, 2013; Mayer and Bukau, 2005, Meimaridou, 2009). A list of wide variety of chemical scaffolds like polyamines, fatty acids, sulfoglycolipids, adenosines and peptideshave been identified which show remarkable affinity for HSPs (Evans et al., 2010).

In stress conditions, HSPs are up-regulated and play an important role in cellular repair and protective mechanisms. For example, they bind as well as refold the denatured proteins due to be in stress, whereas in unstressed normal conditions, they perform their routine works like proper folding, assembly, and intercellular trafficking of newly synthesized proteins (Becker and Craig, 1994; Hartl, 1996, Lindquist and Craig, 1988).

Physiological relevance of the TLQP-21 and HSPA8 interaction

Although it was unanticipated at first sight that HSPA8 be a receptor for TLQP-21, this was consistent with several earlier and very recent findings.

Obesity and diabetes

First, expression of HSPA8 has been found to increase in association with obesity and diabetes (Tiss et al., 2014). Increased expression of HSPs is required in persons with obesity to minimize inflammatory and metabolic stresses imposed by obesity. HSPs are believed to play crucial role in renovating cellular and metabolic homeostasis (McArdle et al., 2002; Morton et al., 2006) by decreasing inflammation, uprising skeletal muscle oxidation (Morino et al., 2008; Gupte et al., 2009; Liu et al., 2012; Henstridge et al., 2014).

In consistent with the finding of less expression of HSPs in T2DM (Kurucz et al., 2002; Bruce et al., 2003); HSPs have been considered with importance for the treatment of insulin resistance and obesity related T2DM (Chung et al., 2008; Literati-Nagy et al., 2009). In fact, the role of HSPs was under-recognized previously in the maintenance of homeostasis in the physiology, with reference to the obesity-driven inflammation that promotes insulin resistance (Hooper and Hooper, 2009). All these lend support to the argument in favour of a TLQP21-HSPA8 connection in modulating obesity. In this respect, it should be remembered that TLQP-21 is the first identified VGF-derived peptide involved in energy homeostasis (Bartolomucci et al., 2007) and considered as putative target to treat obesity related disorders (Cero et al., 2014) as its role in diabetes (Zhang et al., 2013; Stephens et al., 2012), hypertension (Fargali et al., 2014) and lypolysis (Possenti et al., 2012) has already been confirmed.

Metabolism

TLQP-21 exerts important effects on energy metabolism, its administration decreased food intake and increased energy expenditure in Siberian hamsters (Jethwa et al., 2007). It also decreased body weight and WAT in mice fed high fat diet for 14 days, blocking hormonal changes associated with this diet and provoking the autonomic activation of the adrenal medulla and adipose tissue. Furthermore, intracerebroventricular administration of TLQP-21 reduced early phase diet induced obesity (Bartolomucci et al., 2006). It is therefore noteworthy that expression of HSPA8 has been shown to be modulated by diet. Thus, significant downregulation was seen in liver from rats fed high-fat sucrose diet versus starch-rich control diet (Bondia-Pons et al., 2011), and in response to increased bean consumption (Daniell et al., 2012).

Reproduction

Another argument favoring the physiological relevance of this newly discovered TLQP 21/HSPA8, ligand-receptor relationship comes from the study of reproduction. HSPA8 contributes to survival of sperm in the oviduct (Elliott et al., 2009). And enhances the ability of spermatozoa to bind oviductal epithelial cells, boosting up in-vitro fertilization performance (Moein-Vaziri et al., 2014). Furthermore, HSPA8 has crucial protective functions in the process of spermatogenesis and epididymal maturation of male germ

cells under stress conditions (Zaprjanova et al., 2013). SRY (sex determining region on the Y chromosome) plays a key role in mammalian sex determination within the nucleus. HSPA8 plays a key role in calcium-binding protein, calmodulin (CaM) dependent nuclear import of SRY (Kaur et al., 2013). On the other hand, after administration of TLQP-21 on adolescent males with chronic food deprivation, the gonadotrophin response of hyphothalamic-pituitary-gonadal (HPG) axis was found to be reduced and in fed males it caused puberty delay (Pinilla et al., 2011), consistent with the infertility found in male VGF knockout mice (Hahm et al., 1999; 2002).

Gastric acid discharge

HSPA8 was reported to be involved in the healing of acetic acid-induced gastric ulcers in rats. The protein was expressed highly in the normal mucosa and ulcerated tissue, though the level of protein expression was not changed during the ulceration and ulcer healing process (Tsukimi et al., 2001). Remarkably, the central inhibitory effect of TLQP-21 on gastric acid secretion was proved, confirming that it is mediated by endogenous somatostatin and prostaglandins and requires the integrity of sensory nerve fibres (Sibilia et al., 2012).

Hypertension

Altered gene expression of HSPA8 was also found to be involved in hypertension in patients with blood-stasis syndrome (Lian et al., 2014), in Japaneese individuals with chronic kidney disease (Oguri et al., 2009), patients with thoracic aortic aneurysm (Kato et al, 2008), patients with arterial hypertension (Timofeeva et al., 2006). The findings that acute and chronic administration of the VGF-derived peptide TLQP-21 to rodents improved hypertension (Fargali et al., 2014) indicates that the action of TLQP 21 may be mediated by the receptor HSPA8.

Survival and proliferation of cells

At this stage, it is difficult and premature to conclude whether binding of TLQP-21 to cell surface HSPA8 has a positive or negative effect for the survival and proliferation of SH-SY5Y cells. On the one hand, it might result to activation of signals leading to proliferation, perhaps by activating some secondary membrane partner bound to HSPA8. This would be consistent with the general neurotrophic character of VGF and its derived peptides. Simultaneous targeting of HSPA8 and HSP1A induces tumor-specific apoptosis (Powers et al., 2008), which highlights the important role of HSPA8 in viability of tumor cells.

Concluding remarks and future directions

The findings highlighting the physiological relevance of the HSPA8 and TLQP-21 connection give more credence to the interaction of HSPA8 and TLQP-21 or at least the probable involvement of HSPA8 in TLQP-21 induced biological actions. In fact, due to all these physiological relevancies of HSPA8 and TLQP-21, it is highly likely that the HSPA8-TLQP-21 interaction prompts various cellular responses, though the consequences of HSPA8-TLQP-21 are still elusive and need more clarification in signaling pathways.

What is now left and of upmost important in the field of HSPA8-TLQP-21 interaction is complete elucidation of physiologically important downstream signaling pathways with further characterization. The further read out of TLQP-21 signaling can be exploited to explore new horizon in diagnosis and therapies for TLQP-21 related human diseases, especially in which it has been shown to have effect and related with thereof, notably metabolism, gastric acid secretion, reproduction, hypertension, lipolysis, Obesity, diabetes (as mentioned above).

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