Available online at www.sciencedirect.com
ScienceDirect
Mechanisms of Ageing and Development 128 (2007) 125–136
Mechanisms of Ageing and Development
www.elsevier.com/locate/mechagedev

Chaperonomics, a new tool to study ageing and associated diseases

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Available online 22 November 2006

Abstract

The participation of molecular chaperones in the process of senescence and in the mechanisms of age-related diseases is currently under investigation in many laboratories. However, accurate, complete information about the number and diversity of chaperone genes in any given genome is scarce. Consequently, the results of efforts aimed at elucidating the role of chaperones in ageing and disease are often confusing and contradictory. To remedy this situation, we have developed chaperonomics, including means to identify and characterize chaperone genes and their families applicable to humans and model organisms. The problem is difficult because in eukaryotic organisms chaperones have evolved into complex multi-gene families. For instance, the occurrence of multiple paralogs in a single genome makes it difficult to interpret results if consideration is not given to the fact that similar but distinct chaperone genes can be differentially expressed in separate cellular compartments, tissues, and developmental stages. The availability of complete genome sequences allows implementation of chaperonomics with the purpose of understanding the composition of chaperone families in all cell compartments, their evolutionary and functional relations and, ultimately, their role in pathogenesis. Here, we present a series of concatenated, complementary procedures for identifying, characterizing, and classifying chaperone genes in genomes and for elucidating evolutionary relations and structural features useful in predicting functional properties. We illustrate the procedures with applications to the complex family of *hsp70* genes and show that the kind of data obtained can provide a solid basis for future research.

Keywords: Molecular chaperones; Chaperonopathies; Ageing; Chaperonomics; Hsp70; Bioinformatics analysis

1. Introduction

Molecular chaperones have been known for 40 years, and have been extensively investigated, particularly in the last two decades. However, few systematic attempts have been made to organize the knowledge about chaperones within a single, comprehensive, and coherent body, representing a recognizable academic field and a scientific discipline with defined subject matter and distinguishing characteristics. The time has arrived to introduce chaperonology, the field of science that studies molecular chaperones.

This article is one of a few, some already published (e.g., Macario and Conway de Macario, 2005) and others to follow soon that present the chaperonology concept and outline its scope and contents.

Chaperonology encompasses the study of normal and abnormal chaperones in all aspects of structure and function. It also includes the study of chaperone genes in genomes, i.e., chaperonomics; the identification and characterization of deficient, pathologic chaperones, namely the chaperonopathies; and the development of means to use chaperone genes and their products for preventing and treating disease, i.e., chaperonotherapy.

In recent times, evidence has been gathered showing that defective chaperone molecules disrupt cellular functions, leading to cell, tissue, and organismal pathology (Macario and Conway de Macario, 2005; Nardai et al., 2006). Furthermore, defective chaperones have been implicated in the process of ageing and its associated diseases (Soti and Csermely, 2000, 2003; Nardai et al., 2002; Macario and Conway de Macario, 2002). The pathologic conditions, in which sick chaperones play a central or an auxiliary pathogenetic role, have been grouped under the name of chaperonopathies (Macario and Conway de Macario, 2002, 2004).

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0047-6374/$ – see front matter
doi:10.1016/j.mad.2006.11.019

To study chaperonopathies and their role in ageing, and understand their mechanisms with the view of developing specific preventive and therapeutic means, it is convenient or even necessary to (a) identify the full complement of chaperone genes in the genome of the organism of interest, (b) investigate the pattern of expression of these genes and, since there are several chaperone families with multiple members each, (c) elucidate the specific function(s) of each gene within each family.

This article deals with chaperonomics (Macario et al., 2005). Since complete genome sequences began to be published, it became possible, and to some extent necessary, to examine genomes before embarking in the detailed experimental or clinical investigation of any gene or group of genes of interest to biologists, pathologists, and clinicians. This principle applies also to the analysis of chaperone genes and proteins. Thus, it has become necessary to develop new methods, and to adapt and standardize already described methods, for the specific

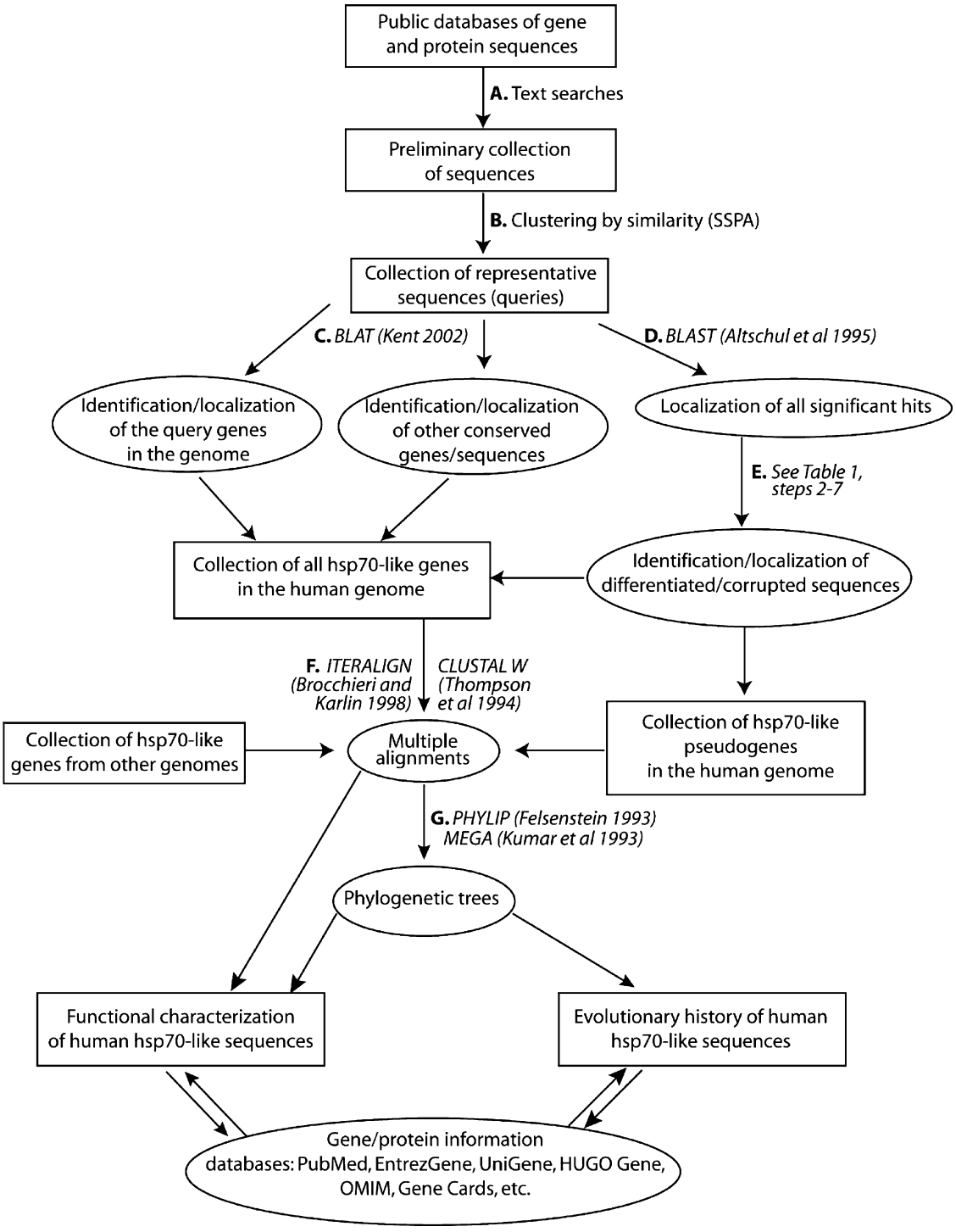

Fig. 1. Multistage procedural sequence developed for chaperonomics as it was applied to the identification and characterization of *hsp70* genes in the human genome.