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The implications of gene heterozygosity for protein folding and protein turnover

Brian R. Ginn

Department of Biology, School of Biology, Georgia Institute of Technology, 310 Ferst Dr., Atlanta, GA 30332, United States

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ABSTRACT

The offspring of closely related parents often suffer from inbreeding depression, sometimes resulting in a slower growth rate for inbred offspring relative to non-inbred offspring. Previous research has shown that some of the slower growth rate of inbred organisms can be attributed to the inbred organisms' increased levels of protein turnover. This paper attempts to show that the higher levels of protein turnover among inbred organisms can be attributed to accumulations of misfolded and aggregated proteins that require degradation by the inbred organisms' protein quality control systems. The accumulation of misfolded and aggregated proteins within inbred organisms are the result of more negative free energies of folding for proteins encoded at homozygous gene loci and higher concentrations of potentially aggregating non-native protein species within the cell. The theory presented here makes several quantitative predictions that suggest a connection between protein misfolding/aggregation and polyploidy that can be tested by future research.

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1. Introduction

The offspring of distantly related parents are usually larger and healthier than the offspring of closely related parents. This phenomenon is called heterosis. Many hypotheses have been provided to explain heterosis including dominance theory, over-dominance theory, and epistasis (Li et al., 2001). There is experimental evidence that supports each of these hypotheses, and all of the hypotheses are thought to explain different aspects of heterosis.

Dominance theory attributes heterosis to the complementation of deleterious recessive alleles by superior dominant alleles (Davenport, 1908; Bruce, 1910; Jones, 1917). Inbred lines are assumed to be homozygous for deleterious recessive alleles at different gene loci. The offspring of the crossed inbred lines are then less likely to be homozygous for deleterious recessive alleles at any given gene locus. Over-dominance theory attributes heterosis directly to the presence of co-dominant alleles at each gene locus (Shull, 1908; East, 1936). Each inbred line is homozygous for alleles that perform well by themselves, but the combined action of the co-dominant alleles results in superior offspring when the inbred lines are crossed. Epistasis attributes heterosis to the interactions between different alleles at different gene loci (Yu et al., 1997; Luo et al., 2001).

One epistasis-type hypothesis for heterosis is the metabolic efficiency hypothesis. Data reported in Hawkins et al. (1986) and substantiated by other studies (Mitton and Koehn, 1985; Danzmann et al., 1987; Mitton, 1993; Hedgecock et al., 1996; Pogson and Fevolden, 1998; Bayne et al., 1999; Hawkins and Day, 1999; Bayne, 2004; Borrell et al., 2004; Pujolar et al., 2005) indicate that inbred organisms are less metabolically efficient than non-inbred organisms. This may be attributable to inbred organisms having increased rates of protein turnover relative to non-inbred organisms (Hawkins et al.,1986; Hedgecock et al., 1996; Bayne, 2004). By definition, inbred organisms must then have increased rates of protein synthesis balanced by increased rates of protein degradation. Since both protein synthesis and degradation are energy consuming processes, inbred organisms must consume more energy to sustain a given biomass, and are thus less "metabolically efficient." The hypothesis then argues that inbred organisms have slower growth rates than non-inbred organisms because more of the energy they consume must go into maintenance, leaving less energy available for synthesis of additional biomass. The metabolic efficiency hypothesis ties into another debate held among population geneticists over the cause and significance of correlations between multi-locus heterozygosity and fitness related traits such as growth rate, viability, and fecundity (Mitton, 1978; Koehn and Hilbish, 1987; Borrell et al., 2004).

The main strength of the metabolic efficiency hypothesis is that it is based on measurements performed under controlled conditions, but it does have weaknesses. The metabolic efficiency hypothesis does not explain why inbred organisms are less healthy than non-inbred organisms. It only attempts to explain the reduced body size and slower growth rates of inbred organisms relative to their non-inbred counterparts. Another

E-mail address: bginn3@gmail.com

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weakness of the metabolic efficiency hypothesis is that it is completely empirical. There is no theoretical explanation for why inbred organisms have higher rates of protein turnover than non-inbreds (Hawkins and Day, 1999; Borrell et al., 2004). This paper attempts to provide an explanation of the reduced metabolic efficiency of inbred organisms in terms of the thermodynamics of protein folding and its impact on protein quality control.

1.1. Protein stability

One of the driving forces of the protein folding process is the hydrophobic effect (Anfinsen, 1973; Chandler, 2002; Rocha et al., 2004; Berne et al., 2009). Proteins contain a hydrophobic core of non-polar amino acids that interact weakly with water and are, consequently, driven into the interior of the protein (Nozaki and Tanford, 1971). This hydrophobic repulsion is the result of free energy changes that occur in water molecules that surround the non-polar regions of a polypeptide chain (Kauzmann, 1959; Tanford, 1980; Chandler, 2002). The water molecules are oriented so as to minimize interactions with the non-polar polypeptide chain regions and maximize interactions with surrounding water molecules, thereby, increasing their free energy value relative to the water molecules in the bulk media (Xu and Berne, 2001; Perera et al., 2009. The number of hydration shell water molecules is reduced when the hydrophobic regions are pushed into the interior of the folded protein. The freed water molecules then pass into the bulk media and attain a lower free energy value (Tanford, 1980; Chandler, 2002; Berne et al., 2009).

Many attempts have been made to validate the theory of the hydrophobic effect by measuring the dynamics of the water molecules in the vicinity of folded and unfolded proteins. However, there is still much debate on the structure and behavior of hydration shell waters (Halle, 2004; Bagchi, 2005). The consensus view is that a protein's hydration shell consists of 2–3 layers of water molecules and extends about 10 Å from the protein surface (Halle, 2004; Bagchi, 2005). The hydration shell was originally proposed to be an ice-like cage that extends outward from the protein surface (Frank and Evans, 1945). However, recent studies have modified this view substantially (reviewed in Halle, 2004; Bagchi, 2005; Rashke, 2006). Ample evidence from various spectroscopy techniques and molecular dynamics simulations indicate that the translational and rotational motions of hydration shell water molecules are slower than the motions of bulk water molecules, but the hydration shell water molecules are too dynamic to be considered "ice-like". NMR and molecular dynamics techniques show only a modest 2–3-fold slowing of hydration shell water dynamics relative to bulk water (Marchi et al., 2002; Pizzitutti et al., 2007; Kuffel and Zielkiewicz, 2008; Halle and Nilsson, 2009). On the other hand, time resolved fluorescence methods and mid-infrared pump-probe spectroscopy have found bimodal behavior of hydration shell water molecules. The water molecules occupying the innermost shell are slower than bulk water by 1 or 2 orders of magnitude while the water molecules occupying the peripheral shell are only slightly slower than bulk water (Bizzarri and Cannistraro, 2002; Pal et al., 2002; Peon et al., 2002; Bhattacharyya et al., 2003; Rezus and Bakker, 2008; Petersen et al., 2009). The discrepancy between these techniques is a matter of debate (Qiu et al., 2006; Qvist and Halle, 2008; Halle and Nilsson, 2009; Laage et al., 2009; Petersen et al., 2009; Zhang et al., 2009). Nevertheless, even the reports of slow dynamics are more similar to supercooled water than ice (Bizzarri and Cannistraro, 2002; Russo et al., 2004, 2007; Jannson et al., 2005; Chen et al., 2006; Franzese et al., 2008).

Distinguishing the dynamics of water molecules within specific regions of a protein is difficult, but some studies indicate that water molecules in the vicinity of non-polar residues have faster translational and rotational motions than water molecules surrounding polar residues (Xu and Berne, 2001; Russo et al., 2004; Li et al., 2005; Hua et al., 2006; Agarwal et al., 2010). Furthermore, the dynamics of water molecules speed up when proteins loose their native conformation and hydrophobic groups become solvent exposed (Amisha-Kamal et al., 2004; Zhang et al., 2009). The faster dynamics of water molecules in the vicinity of non-polar residues is usually attributed to the absence of hydrogen bonding between the non-polar side chain and the surrounding water molecules (Xu and Berne, 2001). This may indicate that the free energy change associated with the exposure of hydrophobic residues to water has both an enthalpic and entropic component (Chandler, 2002; Berne et al., 2009).

The chief evidence for the importance of the hydrophobic effect comes from site-directed mutagenesis experiments that remove non-polar amino acids from polypeptide chains and then measure the reduced stability of folded proteins (Anfensen, 1973; Yutani et al., 1987). The Gibbs free energy of reaction for the protein folding process can be expressed as the sum of the free energy changes of the polypeptide chain and the surrounding water molecules (Rocha et al., 2004):

$$\Delta G^{Folding} = \Delta G^{Chain} + \Delta G^{Water} \quad (1)$$

For convenience, the process of protein folding may sometimes be treated as a simple two-state process, which oversimplifies the complex process of protein folding, but is still useful for understanding the parameters that affect protein stability (Davis-Searles et al., 2001; Fritter, 2003; Chebotareva et al., 2004). In this model the protein can be described as existing in either an unfolded state or a folded state which participates in the reaction: $F \leftrightarrow U$. The equilibrium constant for this reaction may be expresses as (Anson, 1945; Davis-Searles et al., 2001; Schellman, 2003; Chebotareva et al., 2004):

$$\ln K = \ln(C_U/C_F) = -\Delta G^{\circ}/RT \quad (2)$$

where C_U is the concentration of unfolded protein, C_F is the concentration of folded protein, ΔG° is the standard Gibb free energy of unfolding taken from Eq. (1), R is the ideal gas constant, and T is temperature.

1.2. Protein quality control

The two-state model is only accurate for proteins consisting of short polypeptide chains. In reality, most polypeptide chains are so large that there are an enormous number of conformations that the chain could assume if folding were guided by completely random motions (Levinthal, 1968). The fast speed at which proteins spontaneously fold into their native conformations suggests that folding is not random, but rather proteins follow a path towards energy minimization (Chou and Sheraga, 1982; Leopold et al., 1992; Onuchic et al., 1995; Dill et al., 1997). The principle of energy minimization was originally used to predict local structure within the protein such as α-helices and ß-chains (Chou et al., 1983, 1985, 1986, 1992). More recently, energy landscape theory has been developed to capture the complex energetics of protein folding by representing all of the paths a folding polypeptide chain can take to the native state as a 3-D landscape (Onuchic et al., 1997; Plotkin and Onuchic, 2002; Levy and Onuchic, 2006). While the native conformation of the protein represents a global minimum in the energy landscape, there may be other local minima that serve as traps for the folding polypeptide chain. These local minima represent metastable intermediate conformations that the protein may assume for prolonged periods of time instead of the native conformation (Shea et al., 2000; Cheung et al., 2004; Kapon et al., 2008). An

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