Infection, Genetics and Evolution 51 (2017) 245–254

Contents lists available at ScienceDirect

Infection, Genetics and Evolution

journal homepage: www.elsevier.com/locate/meegid

Research paper

From epigenetic landscape to phenotypic fitness landscape: Evolutionary effect of pathogens on host traits

Mark Jayson V. Cortez, Jomar F. Rabajante *, Jerrold M. Tubay, Ariel L. Babierra

Institute of Mathematical Sciences and Physics, University of the Philippines Los Baños, College, Laguna 4031, Philippines

ARTICLE INFO

Article history:
Received 7 May 2016
Received in revised form 3 April 2017
Accepted 6 April 2017
Available online 10 April 2017

Keywords:
Parasitism
Disease
Inclusive inheritance
Biodiversity
Mathematical model
Red Queen

ABSTRACT

The epigenetic landscape illustrates how cells differentiate through the control of gene regulatory networks. Numerous studies have investigated epigenetic gene regulation but there are limited studies on how the epigenetic landscape and the presence of pathogens influence the evolution of host traits. Here, we formulate a multistable decision-switch model involving several phenotypes with the antagonistic influence of parasitism. As expected, pathogens can drive dominant (common) phenotypes to become inferior through negative frequency-dependent selection. Furthermore, novel predictions of our model show that parasitism can steer the dynamics of phenotype specification from multistable equilibrium convergence to oscillations. This oscillatory behavior could explain pathogen-mediated epimutations and excessive phenotypic plasticity. The Red Queen dynamics also occur in certain parameter space of the model, which demonstrates winnerless cyclic phenotype-switching in hosts and in pathogens. The results of our simulations elucidate the association between the epigenetic and phenotypic fitness landscapes and how parasitism facilitates non-genetic phenotypic diversity.

1. Introduction

The mechanisms of epigenetics are multifaceted and complex (Danchin et al., 2011; Gómez-Díaz et al., 2012; Huang, 2013; Duncan et al., 2014; Kilvitis et al., 2014; Skinner, 2015). In spite of numerous experimental and theoretical studies on the epigenetic landscape of phenotype specification (Richards, 2008; Rohlf et al., 2012; Huang, 2013; Kilvitis et al., 2014; Rabajante et al., 2015a), its behavior is not yet fully understood, especially in the presence of pathogens (e.g., parasites). Mathematical models need to advance to capture the important qualitative behavior of the epigenetic landscape that involves many factors, such as diseases that affect phenotype specification and fitness of species (Raghavan et al., 2010; Geoghegan and Spencer, 2012; Huang, 2012; Rabajante and Babierra, 2015; Rabajante et al., 2015a). Parasitism-mediated alterations in population epigenetics have not gained high attention in computational systems biology (Poulin and Thomas, 2008; Boyko and Kovalchuk, 2011; Bierne et al., 2012; Gómez-Díaz et al., 2012). Theoretical predictions that employ epigenetic perspective can guide ecological, agricultural, epidemiological and biomedical studies in investigating the implications of host-pathogen interaction in phenotype variation and trait heritability (Woolhouse et al., 2002; Mallard and Wilkie, 2007; Poulin and Thomas, 2008; Kasuga and Gijzen, 2013; Rabajante et al., 2015a). Epigenetics should be integrated to the study of parasite-induced evolution since the epigenetic pattern (epigenotype) in host gene expression is a non-genetic factor that can be inherited from parents to offspring (Pál and Miklós, 1999; Bond and Finnegan, 2007; Bonduriansky and Day, 2009; Petronis, 2010; Danchin et al., 2011; Kilvitis et al., 2014; English et al., 2015).

Our approach uses mathematical modeling in investigating host-parasite interactions. We introduce the concept of epigenetic attractors and host-parasite coevolution in the following subsections. These concepts are important in addressing the gap between the study of epigenetic landscape at the individual (organism) level and the study of host phenotypic fitness landscape at the population level. In the development of our model, we start at the cellular level since the trait of an organism is reflective of the phenotype expressed by its cells.

1.1. Epigenetic attractors

Mathematical models of epigenetic landscape describe cell-fate determination or specification as a process converging to cellular 'attractors' (Cinquin and Demongeot, 2005; Huang, 2012; Furusawa and Kaneko, 2012; Huang, 2013; Rabajante and Babierra, 2015; Rabajante and Talaue, 2015). Stem cell differentiation is illustrated as a branching progression from totipotency and pluripotency to various cell lineages to different terminally specialized cell types (see individual epigenetic landscapes in Fig. 1) (Furusawa and Kaneko, 2012; Huang,

* Corresponding author.
E-mail address: jfrabajante@up.edu.ph (J.F. Rabajante).

http://dx.doi.org/10.1016/j.meegid.2017.04.006
1567-1348/

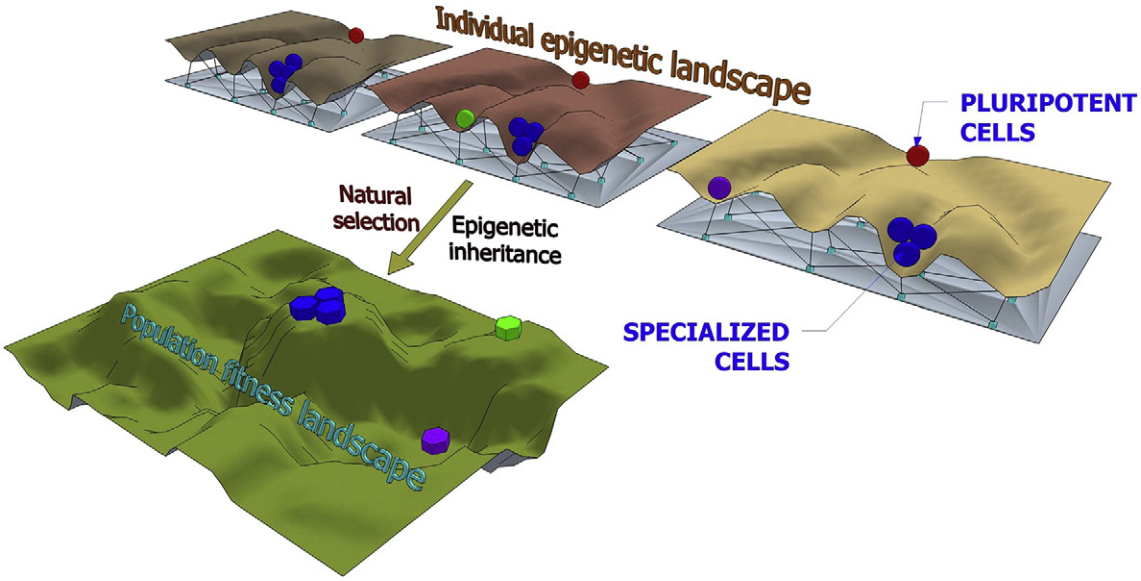

Fig. 1. The link between the epigenetic landscape and fitness landscape. In this study, natural selection (e.g., negative frequency-dependent selection) is induced by environmental or external factors, such as pathogens. Epigenetically controlled developmental plasticity, which is influenced by parasitism, is a major source of phenotypic diversity in a population. We assume that the collective dynamics of the individual epigenetic landscapes are reflected in the phenotypic fitness landscape at the population level through epigenetic inheritance and parasitism-induced selection. If a phenotype is advantageous for survival and there is robust epigenetic memory, a population of species may select this phenotype resulting in higher phenotypic fitness. Note that in an epigenetic landscape, stable cellular attractors can be found in the valleys, and the stable attractors are separated by the ridges. On the other hand, a hilltop (local maxima) in the phenotypic fitness landscape represents higher fitness compared to the valleys.

2013; Rabajante and Babierra, 2015). Through the regulation of gene interaction, cells "decide" where to converge from among the attractors present in the epigenetic landscape. An attractor can be any fate of the cell (e.g., metastable, terminally specialized, cancer, quiescent, senescence and apoptotic states) (Furusawa and Kaneko, 2012; Huang, 2013; Li and Wang, 2014; Marco et al., 2014; Rabajante and Babierra, 2015; Rabajante et al., 2015a). Metastable states could be totipotent, pluripotent, multipotent or progenitor. The attractors that characterize terminally specialized cells represent different phenotypic fates (e.g., muscle, skin, blood, neuron, bone, fat).

Cell differentiation may not follow a one-directional linear pathway in the epigenetic landscape, that is, the pathway can be multidirectional or circular (Enver et al., 2009; Furusawa and Kaneko, 2012; Rabajante and Babierra, 2015). Cells are said to be plastic and can be driven to undergo dedifferentiation (cells regress to earlier state, e.g., from specialized cells back to pluripotent state) and transdifferentiation (cells transfer to other lineages, e.g., from mesenchymal to neural lineage) (Jopling et al., 2011; Xu et al., 2014). Biological noise and induction by external stimuli may also affect the direction of the developing cells (Rabajante and Babierra, 2015; Rabajante and Talaue, 2015).

The concept of cellular attractor is evolving and has various interpretations. A general rule for being an attractor is that the trajectory of developing cells in the epigenetic landscape from a neighborhood of initial conditions (basin of attraction) should converge to this attractor state (Huang, 2012). Each attractor has its own basin of attraction of different sizes. Any perturbation within the basin of attraction should not result in instability, that is, the state is resilient and homeostatic (Huang, 2013). In a mathematical model, an attractor can be a stable equilibrium point (Huang, 2013; Rabajante and Babierra, 2015), stable limit cycle (Rabajante and Babierra, 2015), strange chaotic attractor (Furusawa and Kaneko, 2012) or noisy attractor (Huang, 2009). Moreover, the parameter values in the mathematical models are dictated by the genes and their interactions (the pegs and strings at the bottom of the individual epigenetic landscapes in Fig. 1 represent gene interaction). Gene interaction is not static but rather dynamic (Rabajante and Babierra, 2015). Modification in the parameter values may result in bifurcation that transforms the topography of the epigenetic landscape to form a new attractor or obliterate an existing attractor (Huang, 2013; Rabajante and Talaue, 2015). Dynamically changing a parameter value could lead cells to change fates by moving their trajectory from one basin of attraction to another (Rabajante and Talaue, 2015).

1.2. Host-parasite coevolution

The interaction and coevolution between hosts and parasites have been widely investigated. In evolutionary biology, arms race competition and the Red Queen dynamics have been hypothesized to cause coadaptation or coevolution in hosts and pathogens (Avrani et al., 2012; Brockhurst et al., 2014; Råberg et al., 2014; Rabajante et al., 2015b; Voje et al., 2015). For the host to survive parasitism, it increases its defense traits; but for the pathogen that relies heavily on the host, it needs to counteract the host defense and increase its pathogenicity. This may result in an arms race competition (Brockhurst et al., 2014; Rabajante et al., 2015b). In several cases where there are multiple types of hosts, parasitism can decrease the abundance of the common host type permitting a rare type to become the new dominant (negative frequency-dependent selection). Common host types, especially monocultures, are more susceptible to the attack of pathogens. This phenomenon is akin to the 'killing the winner' hypothesis (Avrani et al., 2012; Rabajante et al., 2015b). Host-pathogen interaction is one of the explanations for the extinction and diversity of species (Miura et al., 2006; Brockhurst et al., 2014).

Persistence of negative frequency-dependent selection could result in fluctuating Red Queen dynamics, which is illustrated by never-ending cyclic phenotype-switching (Brockhurst et al., 2014; Rabajante et al., 2015b). This phenomenon is characterized by winnerless arms race competition between hosts and parasites. Moreover, the fluctuating Red Queen dynamics is a candidate model of recurrent punctuated equilibrium process that is driven by biotic interaction (Rabajante et al., 2015b). This recurrent punctuated equilibrium process has out-of-phase 'heteroclinic' cycles of rapid negative frequency-dependent