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Finding Biological Roles of Averaging Effect of Large Numbers: The Existence of Genome Vehicles Guiding Cell Fate Decision

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It is intriguing to grasp how a specific path can be chosen by a cell having enormous number of molecules, among vast number of possibilities that can arise, through the complex multi-molecular interactions during cellular process such as differentiation. The basis for such determinism may stem from the averaging effect ("simple rules", [1-3]) caused by the reduction of response fluctuations at cell population level as suggested by our recent investigations on microarray dataset [4,5]. The phenomena of averaging effect in physical many body systems such as thermodynamics, condensed matter and fluid dynamics have been well studied and understood as mean field theory. However, it remains unclear how the complex and dynamically evolving molecular networks found in biological systems can give rise to a globally coherent orchestrated response revealing the role of averaging effect for important cellular processes such as cell fate decision.

The majority of large-scale gene expression studies have focused on genes with high expression changes or variations to decipher key regulatory processes, since low-level expression changes of genes have been considered as noisy due to the issue of poor signal-to-noise ratio in microarray experiments. This is due to the difficulty in the estimation of unspecific binding abundance between probe and target in signal intensity, and especially for the low level expression changes, the effect of background noises, compared with specific binding activity, is likely larger than that for highly variable genes. To overcome the difficulties of dealing with single gene expression noises, we grouped genes of whole genome into ensembles and analyzed their correlation dynamics based on temporal gene expressions using Pearson correlation (linear correlation) and mutual information (nonlinear correlation). We found that the standard deviation of correlation distributions of gene ensembles reduces when the ensemble size is increased following the inverse square root law.

Through the reduction of correlation fluctuations, we deciphered the hidden collective genome-wide average expression dynamics and their roles in two different immune processes, one for the innate immune response of macrophages to lipopolysaccharide (LPS) and another for the neutrophil differentiation process of HL-60 cells for alltrans-retinoic acid (atRA) and dimethyl sulfoxide (DMSO) stimuli:

i) For LPS response, the ensemble property, in wildtype and mutant conditions (MyD88 knockout (KO), TRIF KO, and TRIF & MyD88 Double KO (DKO)), uncovered local and global effects of LPS; local being the well-known pro-inflammatory response of a small number of (about one to two hundred) highly expressed genes (acute mode), while global being the novel collective activation of diverse processes comprising the rest of majority number of the lowly expressed genes (collective mode) [4,6]. The global property of the immune response emerged as a result of the transition from large scatter in expression distributions for single gene to smooth linear lines for grouped genes which can be linearly superposed to decipher the global gene regulatory differential control principle of the transcriptional and mRNA decay machineries between wildtype and mutant genomes. These works also have shed new light on innate immune response, providing significance role of lowly expressed genes in diverse collective mode, which are often considered as noisy and insignificant in microarray experiments. Notably, the strong invariance (i.e., very high linear correlation > 0.98) between whole genome expressions in different mutant conditions of the same cell-type, can be considered as a sort of dynamical attractor encompassing the entire transcriptome, reflecting hidden genome-wide differential regulations [7].

ii) Elucidating further understanding of significance role of the global response [6], our study on neutrophil differentiation showed despite initial differences of the transcriptional program induced by atRA and DMSO stimulations, the two probability distributions of correlations of randomly selected genes for atRA and DMSO responses overlapped after 48 hours defining the neutrophil attractor. Tracking the ensembles' trajectories, we noticed that only certain, not all, fall into the attractor in a fractal-like manner. The removal of these genome elements from the whole

genomes, for both atRA and DMSO responses, destroys the attractor providing evidence for the existence of specific genome elements (named "genome vehicle") responsible for the neutrophil attractor. Selective portions of fractal-like gene ensembles are responsible for the neutrophil cell fate decision acting as 'drivers' of the reaching of a subsequent genome-wide characteristic profile [5].

Conclusions

We showed the existence of averaging effect of large numbers in two distinct immune processes and their biological roles. In LPS stimulated innate immune response, our works points to the presence of a highly-ordered, coordinated, genome-wide expression dynamics of LPS stimulation, thereby requesting the need to consider global phenomena when interpreting immune response. On the other hand, in neutrophil differentiation, we showed the self-regulation of the genome vehicles leads to the formation of a common neutrophil attractor for neutrophil differentiation process. In addition, we demonstrate that the collective motion of lowly and moderately variable genes within the genome vehicle, which are often considered as noisy and insignificant, play an important role in the formation of the neutrophil attractor, perhaps indicating the non-instructive signaling of genes related to small-amplitude DNA motions [8,9]. Since the dynamics of gene expression is connected with the dynamics of chromatin structural changes, finding the underlying mechanisms, such as the collective dynamics of small-amplitude DNA fluctuations within chromatin structure, for the motion of the genome vehicle might decipher fluctuations in chromatin dynamics that determines cell fate decision. It will be interesting to know how the concerted motion of the genome vehicle, together with well-known master instructive genes, such as Yamanaka factors [10], drives the differentiation of pluripotent stem cells as well as the emergency of cancer stem cells and other biological processes that could acquire a completely different perspective under the proposed model.

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