

Self-organisation of early stress response in the biology of cancer

Letter to the Editor

ABSTRACT

The early stress response by AP-1 (FOS/JUN), supported by upregulation of c-Myc and involved in cell-fate changes and adaptation to hostile environments, is increased in cancer. The review shows the biphasic character of this response with negative feedback typically lasting a few hours as a feature of the genome regulation by self-organising criticality. It involves the rapid splitting of the pericentromeric heterochromatin clusters, the opening of the active chromatin, and a massive transcription acceleration wave. Phylostratigraphic analysis revealed that AP-1 genes evolved in the Cambrian explosion ~500 Mya integrating the protein interaction networks of reproduction including proto-placenta intertwined with cytokine and immunity pathways, sex determination, oocyte maturation, and embryonal stemness. The peak of this response as part of accelerated cell senescence led by AP-1 and IL-1 β was found in the breast cancer cell line resistant to doxorubicin. The adaptability of aggressive cancer to treatments can be explained by emergent stress response evolutionarily protecting reproduction.

INTRODUCTION

The attempts of 20th-century researchers to understand cancer and find causal treatments from the viewpoint of the somatic mutation theory coupled with the Darwinian selection of the fittest clones largely failed after the cancer genome sequencing project. As recognised by the world leader in cancer research Robert Weinberg, cancer turned out to be more complex than it was initially thought [1]. Furthermore, Mechlav Horazy with Ronald Hancock wrote that the translational research in medical science is lost in the biological complexity, which necessitates the approach of Systems Biology [2]. Professor Ronald Hancock, to whose memory this issue is devoted, did a fantastic work by introducing the idea of the macromolecular crowding in the cell nucleus which dictates regulation by self-organisation. In this mini-review, we attempt to formulate some ideas based partly on the experiments from our laboratory, with a Systems view on self-organisation. It concerns the leading role of the early stress response as a general mechanism that explains the main feature of metastatic, incurable cancer – its high adaptivity to treatments.

THE GENERAL CHARACTERISTICS OF AP-1 AND c-MYC

The early stress response, activated from the cell surface by the RAS-MAPK pathway, is regulated by the nuclear integrator transcription factor AP-1, which allows cellular responses to diverse extracellular cues. It provides a general cell reaction for cell-fate change in development, differentiation, and hostile conditions. Recent genome-wide studies have shown that AP-1 principally operates as a remote command by binding to distal enhancers to regulate transcription and placed chromatin architecture dynamics at the heart of AP-1's transcriptional actions, *via* transcription-pioneering-, chromatin remodelling- and chromatin accessibility maintenance effects [3]. At the same time, AP-1 is also involved in several pathologies, including tumour growth [4] and is overexpressed in most cancers [5].

AP-1 is assembled through the dimerisation of the characteristic leucine zipper DNA-binding domains of the FOS and JUN protein family members. Since the discovery of AP-1's involvement in reacting to various surface cytokines, growth factors, as well as bacterial and viral infections, it has been found in association with numerous regulatory and physiological processes, and new relationships are still under investigation.

c-Myc, which is also upregulated in most cancers, in turn, participates in the early stress response upon being induced post-translationally by FOS. c-Myc is also a member of the basic helix-loop-helix leucine zipper protein family. All

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Abbreviations: AP-1 – activator protein of the early (“immediate”) stress response, a dimeric transcription factor; SOC – self-organisation by criticality; PhStr – phylostrata of Life evolution on Earth

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known biological activities of c-Myc require heterodimerization with its activation partner MAX from the same protein family. c-Myc primarily activates up to 15% of all genes in an organism by binding of c-Myc/MAX heterodimers to specific recognition sites (E-box elements) within promoter regions. c-Myc is not an on-off specifier of gene activity, but rather a nonlinear amplifier of expression, acting universally on active genes, except for immediate early genes that are strongly induced before c-Myc [6,7]. The non-linear effect of c-Myc activation on transcription is also achieved through the remodelling and opening of the chromatin by the activation of histone acetylases [8]. Overexpressed c-Myc favours escape from the firm cell cycle control by the circadian clock, leading to polyploidy along with up-regulation of bivalent genes, many of which, such as H-Ras, EGFR and others, are strong cancer drivers [9,10]. c-Myc overexpression also includes a cell shift to the energy-saving aerobic glycolysis (Warburg effect typical of cancer) in hypoxic conditions [11] and increasing stress tolerance to various environmental cues [12]. Together, the three transcription factors FOS, JUN and c-Myc thus provide the generality (Systems character) of the adaptive cell response.

Some more features of this response are important for our current purpose – to show AP-1's participation in critical self-organisation that can provide a rapid non-linear change of the genome expression.

Firstly, both FOS and JUN themselves are short-lived bivalent proteins, possessing both the activating and repressive histone modifications (H3K4me3 and H3K27me9) at the promoters of their genes (which allows rapid ON-OFF shifts), while c-Myc represents a hub regulating several thousand bivalent genes. Importantly, AP-1 and their bivalent targets possess gene sequences for the intrinsically disordered protein domains. Both features enable the reshaping of the pleiotropic adaptive networks of multifaceted functional modules [13] and can trigger cell fate change. The bivalency of AP-1 and the targeted genes thus is associated with the potential of rapid and massive genome reprogram-

ming [9,12,14]. An important characteristic of the early gene response represents its temporal expression known as the 'immediate response' – a rapid but transient transcription reacting to extracellular stimuli [15,16]. AP-1 function and regulation can be seen from different models, some of which are shortly discussed below.

BIPHASIC TEMPORAL EXPRESSION OF AP-1 RESPONSE IN VARIOUS STRESS MODULES

Peripheral blood lymphocytes treated by phytohaemagglutinin. Specific mRNAs for *FOS* and *JUN* were detectable within 30 min after cell activation and reached maximal levels within 2 hours. Both *FOS* and *JUNB* mRNAs returned to pre-activation levels within 6 hours [17]; in our hands at this model, the proportion of activated lymphocytes increased at 30 min nearly 3-fold (from 13± 7% to 33±10%).

In the regenerating mouse liver c-fos and c-jun mRNA levels and transcriptional rates increase within 30 min after partial hepatectomy [18]. Acridine orange DNA structural test shows the chromatin opening within 30 min after operation [19]; it reaches its maximum at 1h post-operation [20].

Heat shock response tested on rat adrenal tissue includes the early high activation of the AP-1 binding to DNA [21].

Stress response and hypoxia. Hypoxia is known as an inducer of cancer metastases [22]. When hypoxic conditions were tested on the HeLa cell line, the transcriptional activation of *FOS* was seen within 15 min, reaching a maximum at 30 min [23].

Regulation of the glucocorticoid receptor (GR) by AP-1. GR is a ligand-activated nuclear transcription factor mediating the diverse physiologic effects of glucocorticoids. Serum stimulation of serum-starved NIH 3T3 cells resulted in a ~188-fold induction of *FOS* mRNA at 30 min and a ~9-fold induction of *JUN* mRNA at 1 h, followed by a two-fold increase in GR mRNA levels at 3–12 h. This induction was

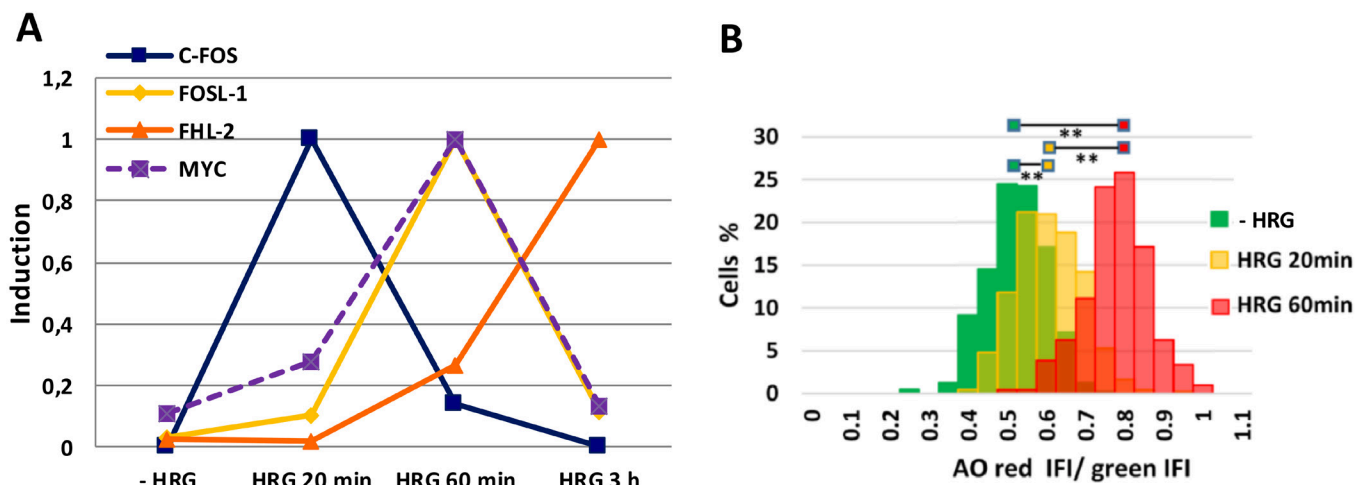


Figure 1. The results of the treatment of MCF-7 cells with heregulin (HRG). (A) Biphasic expression of the early response genes evaluated by qPCR at four-time points normalised to the maximal averaged expression (1 unit on the *y*-axis) of each of the four tested genes (to better visualise the dynamics of response); (B) DNA unfolding induced after 20 and 60 min of HRG treatment in MCF-7 cells related to nontreated starving control (-HRG) as revealed by the Acridine orange DNA structural test by red-to-green fluorescence intensity. The *p*-values were adjusted by multiple *t*-test correction approaches. Republished from [26], CC BY 4.0 licence.

abolished following mutation or deletion of the GR AP-1 binding site from its promoter [24].

Differentiation induction in heregulin-treated breast cancer (MCF7-HRG) model by stress response with features of self-organising criticality. MCF-7 breast cancer cells were treated with heregulin (neuregulin 1) by the protocol providing induction of differentiation (fat production) one to two weeks after treatment [25]. The effects on the gene expression follow the intranuclear transport of EGFR (epidermal growth factor receptor) induced by HRG. In MCF-7 the MAPK pathway activation in 10 min was causing bi-phasic induction of the early stress response genes, the earliest of c-FOS peaking at 30 min followed by its ligand FOSL1 was reported [25]. The sustainability of the FOS and FOSL-1 activation lasting for 1–1.5 hours was critical for differentiation induction. The sequential induction by FOS of FOSL-1 and then FHL2, further induced by interaction of the last two a negative feed-back suppression of FOS with gradual downregulation of MAPK whose activation abated by 3 h, as shown by these authors. In our experiments, we reproduced this bi-phasic stress response and also the following c-Myc peak, all three abated at 3 h (Fig. 1A) [26]. Moreover, we showed that the FOS peak was temporally associated with the opening of the chromatin. This was tested by the negatively charged phosphate residues of the DNA backbone associating with the cationic Acridine orange polymers found shifted at 20 min, but not at 10 min (Fig. 1B). The second shift to the more open chromatin conformation, affecting most nuclei, at 60 min coincided with activation of FOS-L1 and c-Myc (Fig. 1B). The sustainability of the first peak preordained the second [26].

Interestingly, by studying the pericentric heterochromatin domains (PADs) immuno-stained for the H3K9me3 repressive mark and centromeres, we found that this critical point (15–20 min) also coincided with the bursting of PADs (showing in control the power law relationship between their size and number (Fig. 2A). Power law can be heuristically explained as a single long jump. During the same short period between 15 to 20 min of HRG action, acceleration of transcription (Fig. 2B) and transcription fluctuations of a large proportion of genes that represent the features of critical self-organisation (SOC) were found [26].

As can be judged by the similar temporal dynamics of the AP-1 response to various stimuli, partly described above – liver regeneration, influence of hypoxia, heat-shock, activation of lymphocytes by PHA and glucocorticoid nuclear receptors – the study on the MCF7-HRG model reflects the general characteristic of the early stress response. This type of regulation is different from the development occurring by random mutations and Darwinian selection, which is very slow and gradual, due to its rapid and all-or-nothing character and also due to the presence of a second phase – negative feedback.

The arising of “expression waves” marking state transitions related to chromatin structural reorganization through self-organised critical control of whole-genome expression explains the regulation of biological adaptive systems, including the early embryo, living on the edge of chaos [27–

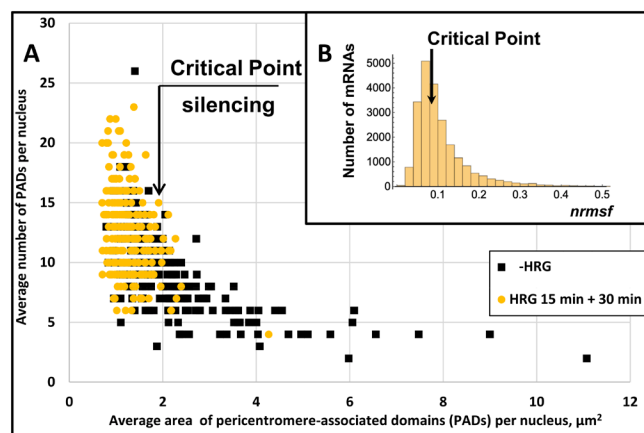


Figure 2. Schematic correlation of data indicating the hypothesis of functional dependency of the heterochromatin reorganization and gene expression. The commitment of differentiation in MCF-7 cells after 15 min of HRG treatment is indicated on both graphs as a Critical Point. (A) Splitting of PADs size under the critical threshold of transcription silencing inducing on (B) the critical acceleration of the whole-genome transcription is shown. Figure fragment for transcriptome data republished from (16) representing transcription speed change (nrmsf) of 22,277 genes shows the critical point at the 15 min of HRG treatment. Republished from [26], CC BY 4.0 licence.

29] and using explorative adaptation, which is particularly evident in cancer [14,30].

It was very interesting to look for the phylogenetic origin of AP-1 which pioneered the adaptive stress response during the life evolution in the human genome.

THE PHYLOGENETIC ORIGIN OF AP-1 RESPONSE IN REPRODUCTIVE PROCESSES

As it is widely assumed that cancer supports its persistence by reproductive cycles [31,32], the bioinformatic phylostratigraphic analysis of 1497 gametogenesis-related genes present in the human genome was performed to investigate their function in the context of evolution. AP-1 was found to have originated in the 8th phylostratigraphic category, or phylostratum (approximately corresponding to the Cambrian explosion circa 500 Mya). By applying STRING network analysis of the protein-protein interactions to the gametogenesis-related genes present in that phylostratum, mostly the “reproductive processes” (GO:0022414) at the level of individual organisms were revealed (Fig. 3).

A gene central to the network, FOS, together with its companion in the AP-1 dimer (JUNB), highlights the early stress response. In the reproductive context, FOS is involved in sex determination critical for the upregulated expression of key ovulatory genes in the ovarian follicle granulosa cells, mediated through hormonal receptors (PGR and EGF) signalling. At the same time, FOS and JUNB are present in the “female pregnancy” GO module (GO:0007565). As such, we can see that FOS unites two somatic modules of reproductive processes: the cluster of endocrine somatic sex determination, on the right, and the proto-placental cluster, on the left.

Str.8

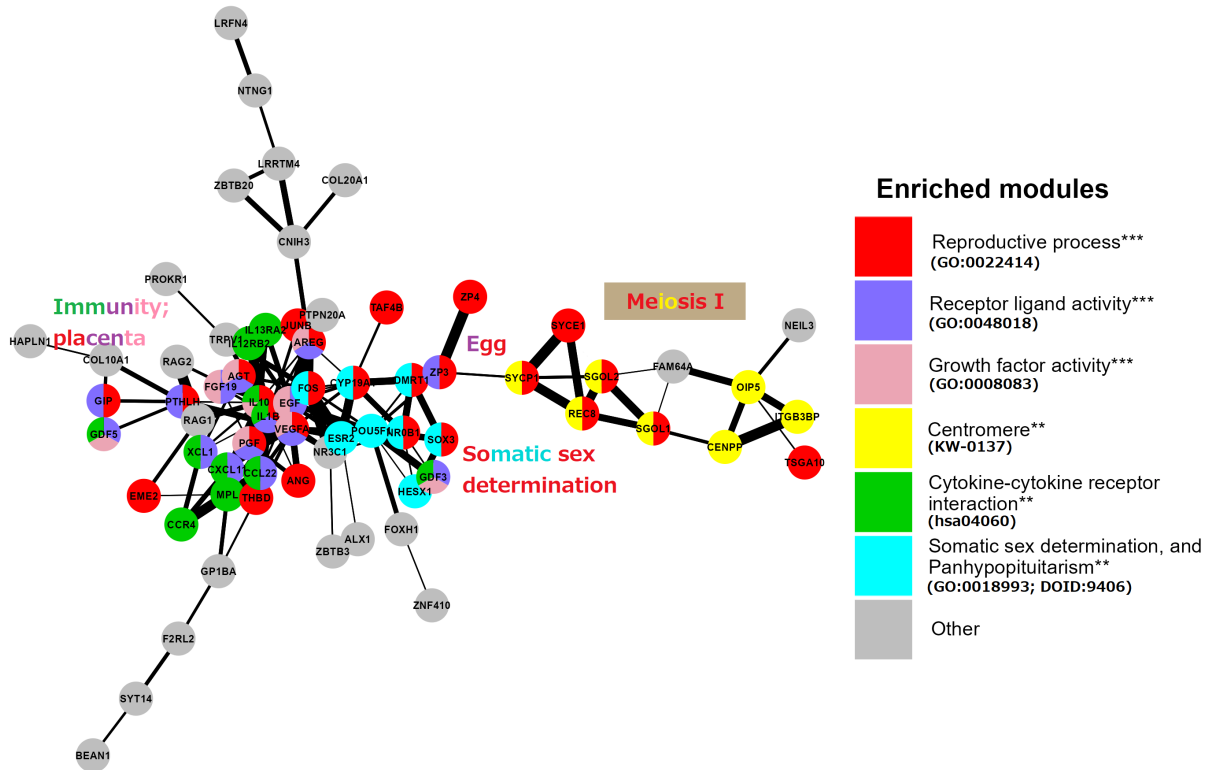


Figure 3. The STRING network of gametogenic genes corresponds to the 8th evolutionary phylostratum of the human genome. Genes (nodes) belonging to enriched functional modules of interest are displayed in the form of pie charts. The main functional modules are also designated by the coloured text (e.g., red – reproductive process, yellow – centromere, etc.). Hypergeometric test ** p -value<0.01; *** p -value<0.001. Republished from [33], CC BY 4.0 licence.

In addition, we found a cluster related to conventional meiosis I. This subnetwork is connected to the ZP3/ZP4 zona pellucida human proteins enclosing the matured oocyte (Egg) and early embryo. Finally, POU5F1, a key to embry-

onic pluripotency and PGC development, is also included in this network [33].

It is interesting to note that the work of [34] also revealed that cell-cell signalling, immunity, and the multicellular stress response appeared at the same period of the multisel-

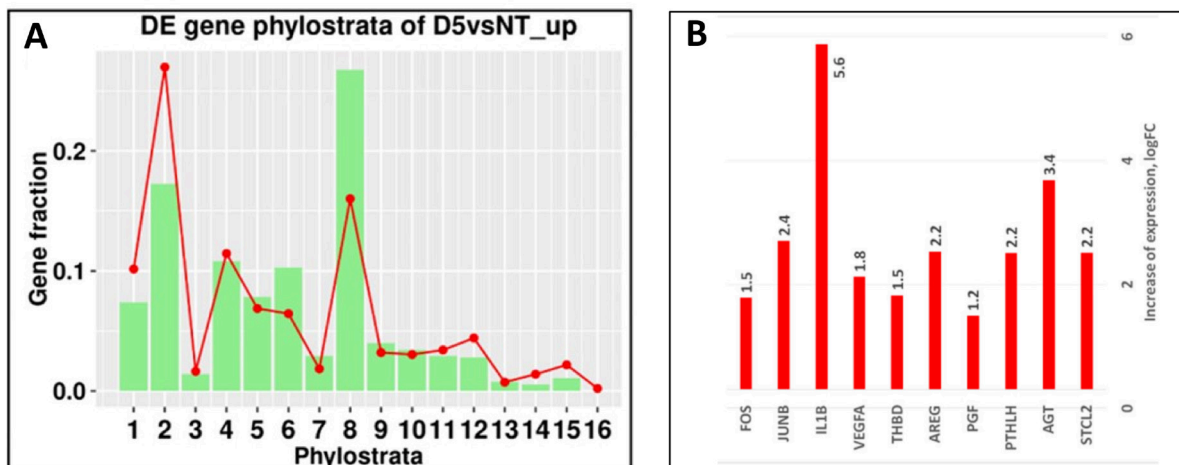


Figure 4. The transcriptome response of MDA-MB-231 cells to 100 nM-24 h Doxorubicin (DOX) treatment sampled on day 5. (A) The DOX-upregulated gene phylostratic distribution (green bars against the red-lined whole-genome reference) showing the strong activation of Str 8 via DOX; DE genes = differentially expressed genes. (B) The “female pregnancy module” upregulated genes (log-folds). They are republished from [33], CC BY 4.0 licence.

lularity development, in the 8th Phylostratum. As a high animal variety of species with different cell fates of individual organism parts, evolved over the surprisingly “short” evolutionarily time of the Cambrian explosion, it likely needed the appearance of the mechanism of emergent self-organisation pioneered by AP-1.

PHYLOGENETIC AP-1-RELATED RESISTANT RESPONSE OF BASAL BREAST CANCER TO CHEMOTHERAPY

Our study on the resistance of the triple-negative breast cancer cell line MDA-MB-231 to chemotherapy (doxorubicin) revealed an upsurge of differentially expressed genes from the phylogenetic stratum 8 belonging to complex animals (Fig. 4A) and in particular the system of embryo invasion and “female pregnancy” (Fig. 4B) [35]. It is pioneered by the AP-1 complex. The genes of the GO “female pregnancy” module – *FOS*, *JUNB*, *IL-1 β* , *VEGFA*, *THBD*, *AREG*, *PGF*, *PTHLH*, and *AGT* – are interlaced there with the immunity network of cell communication and environmental influence by cytokines hubbed by the immunosuppressive cytokine IL-10 and inflammatory IL-1 β and angiogenesis stimulators. The network of this stratum also includes the macrophage differentiation module and T-cell regulation. It may be associated with the repolarisation of tumour-associated macrophages (TAM) towards immune suppression [36,37], in conjunction with the immunosuppressive environment of the placenta.

As related to non-linear thermodynamics, this response was exerted with the background of accelerated cellular senescence (ACS), known to be induced by oncogenes, oxidative stress and anti-cancer treatments [38]. ACS is a bi-stable state characterised by dual expression and competitive feedback between the regulators of quiescence and apoptosis on one side and reprogramming and proliferation, on the other side [30].

In resistant genotoxicity-treated cancer systems, the outcome of survivors is usually low but inevitable [30,39,40]. Therefore, the data of [41] inducing accelerated senescence *in vitro* in WI-38 cells by mutant RAS or RAF gene transfection that showed the pioneering role of the AP-1 complex in this response is highly informative. In line with our findings, the reproductive modules marked by oestrogen and androgen receptors were also found induced there.

CONCLUSION

The difficulty in curing metastatic cancer can be explained by its complexity and high adaptivity due to biological systems operating at the Edge of Chaos [32,42,43].

This complexity is governed by self-organisation pioneered by the early stress response AP-1 complex providing critical (non-linear) genome state transition, which is particularly enhanced after chemotherapy (at least as exemplified). AP-1 is acting *via* transcription-pioneering, chromatin remodelling and chromatin accessibility maintenance effects. It operates with such explorative adaptation tools as bivalency, intrinsically disordered protein domains, alternative splicing, adaptation of the cell cycle checkpoints,

deterioration of circadian rhythms, reversible senescence, PAD splitting and euchromatin opening, depressed immunity, increasing the invasion potential – all of them are put in action through the transient biphasic early stress response.

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