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Opinion

# The GTP Core and Its Regulation in Spatiotemporal Cell Biology

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## Abstract

After a period of more than 50 years, numerous evidences have led to the exploration of the cyclic control core of cells, which sequentially comprise of genomes (G), transcriptomes (T) and proteomes (P). In the previous reports of the investigators on spatiotemporal cell biology, a novel theory system was introduced and reported, and the cyclic control core was named, the "GTP core". Indeed, the GTP core controls all events in cells based on the spatiotemporal cell biology. In the present study, the schematic regulation of the GTP core based on the spatiotemporal cell biology was further discussed and summarized, in order to improve and perfect this novel theory system. It is hope that these perspectives would lead to the further discussion and exploration of this area by other researchers worldwide.

## Introduction

Protein is the only "intelligent molecular worker" molecular type in the body that plays a variety of roles, including executor, performer, regulator and controller. The process, from DNA to functional protein, occurs in the cyclic control core of the body, and this is managed by proteins to establish an accurate and efficient cyclic core system that controls all events in cells. The central dogma of biology is an old theory that has been used for over 50 years to show the complicated molecular regulation events in body. However, in past 50 years, especially in the recent 20 years, with the great advances in bioinformatics and molecule interaction databases, the ability of the central dogma of biology to illustrate or identify regulation methods has become weak, particularly the regulation method of molecular cellular biology based on spatiotemporal cell biology, which was reported by the investigators for the first time in previous studies.[1–3] Furthermore, numerous evidences have led to the exploration of the cyclic control core *in vivo*, which sequentially comprises by three basic parts: genome (G), transcriptome (T) and proteome (P). Indeed, the GTP core is the most basic functional platform reflected in all events in cells or in the body, and this must be accurately regulated based on the spatiotemporal cell biology. Based on reported evidences, the present study summarized the novel insights for GTP core regulation through the triple W[2] and signal basins[3] in spatiotemporal cell biology, in order to improve and perfect this previously reported novel theory system.[1–3]

## The GTP core

The process, from DNA to functional proteins, is the fundamental cyclic dynamic core system in cells and in the body, which includes three basic parts: G, T and P. The investigators named this system, the GTP core. This expands our understanding of the sequential resources and dynamic regulation of the GTP core (Fig. 1a). Indeed, the GTP core controls all events in cells, and this is accurately regulated based on the "Triple W" in spatiotemporal cell biology,[1–3] according to different needs at different time points, places, and cells or individuals (Fig. 1b). The basic executors expressed from each former part comprise of the regulators for the latter part, while the executors expressed by each part are the extended regulators or executors for other events that are not conceptually included in the GTP core (Fig. 2a).

**Keywords:** GTP core; Genome; Transcriptome; Proteome; Spatiotemporal cell biology.

**Abbreviations:** GTP core, core of the genome, transcriptome and proteome; G, genome; Ge, genome extended executors; P, proteome; Pe, proteome extended executors; T, transcriptome; Te, transcriptome extended executors; triple W, when, where and which.

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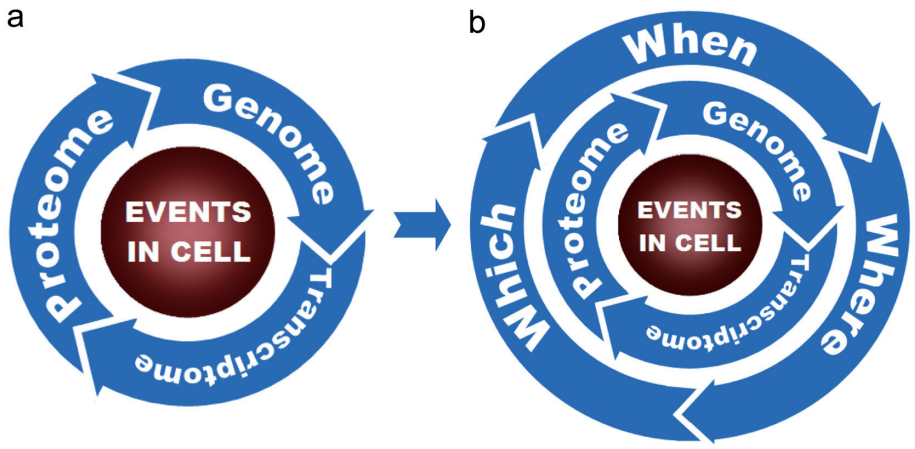


**Fig. 1. GTP core and its cyclic regulation.** A: The GTP core; B: The GTP core in spatiotemporal cell biology. Genome (G): Transcritable and non-transcritable sequences with different modifications (Sequences modified through the epigenetic approach based on the triple W); Transcriptome (T): mRNAs, rRNAs, miRNAs and other ncRNAs (non-coding RNA) with different variations furthered based on the triple W; Proteome (P): All functional proteins and peptides with different ratios or activated levels based on the triple W.

G comprises of parentally inherited sequences, acquired sequence modifications, and epigenetic modifications in postembryonic development (ontogeny), including transcritable and non-transcritable sequences. Furthermore, G is controlled and regulated by genomic regulators, which include transcriptional factors, epigenetic regulators, genomic *trans* or *cis* elements, and other genomic modifiers, and these are "the basic executors for G" at G, while other factors transcripted or expressed in G are considered as "the extended executors for G" as regulators at G and T in the GTP core (genome extended executors, Ge), which support the functions of other parts of the GTP core.

T comprises of mRNAs, rRNAs and non-coding RNAs (ncRNAs). Furthermore, T is controlled and regulated by transcriptomic regulators, including RNA splicers, assemblers and disassemblers, and mRNA degradation regulators, such as miRNAs, ubiquitin and other regulators. All factors mentioned above are "the basic executors for T" at T. The molecules generated or appeared at T such as some ncRNAs (rRNA, tRNA, srpRNA, *etc*.) and others functioning at T and translation are considered as "the extended executors for T" in the GTP core (transcriptome extended executors, Te), which support the function of consequent part of the GTP core.

P comprises of functional proteins and other translated fragments, such as peptides consequent, which include protein manufacturers, helpers, modifiers, and activators/inactivators. All details mentioned above pertain to "the basic extension executors for P" at the translational and post-translational P in the GTP core. Virtually, protein manufacturers, modifiers and helpers are considered as "basic executors for P". Some proteins from P involving the regulation and control of consequent G or T as transcriptional factors or regulators by epigenetics or signal basin following triple W are considered as "the extended executors for P" at the translational and post-translational P in the GTP core (proteome extended executors, Pe), which support the function of other parts of the GTP core.

The description for the regulation of the GTP core is schematically illustrated in Figure 2a.

G represents the initiation part of the cyclic GTP core, and the basic executors for G and Pe understand and use all *trans* or *cis* regulator elements, and other non-transcriptional sequences or factors. Human genome dark matters have consequently been identi-

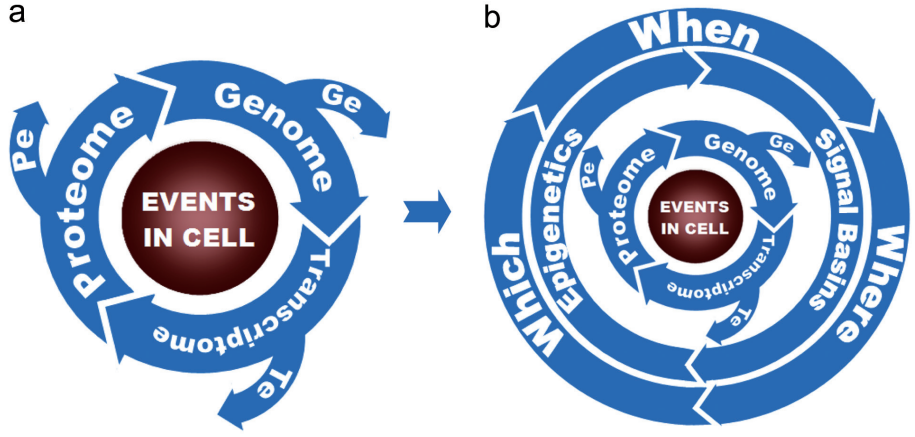


**Fig. 2. Schematic understanding of the regulation of the GTP core based on the triple W in spatiotemporal cell biology.** A: The GTP core, and its executors and extensions; B: The GTP core regulated by signal basins and epigenetics based on the triple W in spatiotemporal cell biology. Ge: Genome extended executors; Te: Transcriptome extended executors; Pe: Proteome extended executors.

fied as ncRNAs, unknown open reading frames (ORFs), and regulatory sequences in G, which are used to determine the regulation of G transcription, druggability and biomarker discovery.[4–8] Some gene loci exert substantial influence on the ability to achieve exceptional results in vitro and in vivo, such as the longevity gene locus at chromosome 4.[9] Modification and regulation by epigenetics are important regulatory approaches for G, which includes promoter and gene body methylation for transcriptional regulation.[10] At this stage, each cell has a choice to use the allele of the maternal or paternal copy of each given autosome pair, which is the fundamental property of chromosomes.[11] The controls described above and others in G form the basic regulation and dynamic drivers for G, which effect or organize all events in the GTP core. The increasing importance of genomics would change the role of genetic evaluation and prediction in clinic.[12]

T is the consequent part after G in the GTP core, and this controlled or executed by T and Ge drivers. These drivers understand and use all transcriptome elements and other factors. SNRPB (small nuclear ribonucleoprotein polypeptides B and B1) is an important member of the basic executors for T, which splices and rearranges mRNAs, and its disruption causes a severe and fatal syndrome (cerebro-costo-mandibular syndrome).[13] Sultan M *et al*.[14] reported a global view of elucidating the functional complexity of the human transcriptome, and they found that 50% of the sequence fragments are mapped to unique genomic locations. Among these, 80% correspond to known exons, in which 66% of the polyadenylated transcriptome are mapped to known genes, while 34% of these are mapped to nonannotated genomic regions. Furthermore, a global survey of mRNA splicing events identified 94,241 splice junctions, and exon skipping was identified as the most prevalent form of alternative splicing.[14] The complexity of the human T and alternative splicing are important approaches by those the structural gene loci in G express a variety of functional proteins, and these were identified to have a number of different families and subfamilies. Wang *et al*. analyzed the deep P and T abundance atlas of 29 healthy human tissues obtained from the Human Protein Atlas, and they found strong differences between mRNA and protein quantities, within and across tissues.[15] These findings show the importance of the basic executors for T and Ge in regulating the GTP core at T. T quality assessment is a crucial step prior to the downstream analysis of novel T and P. This is presently available in domainworld-services.uni-muenster.de/dogma/.[16]

P is the consequent part after T in the GTP core, and is controlled or executed by the basic executors for P and Te, which understand and use all P factors, such as all proteins or peptides that function as regulators for P through interactions with targeting modifications at post-translation. P is characterized by large protein-abundance differences, cell type- and time-dependent expression patterns, and post-translational modifications.[17] RNA-binding P is a special part of P, and an important compositional aspect that addresses the fundamental questions in RNA-biology.[18] Christine Vogel *et al*. conducted P-wide surveys to determine the link with mRNA and protein abundance, and they summarized the major factors for regulating the protein expression.[19] Recent advances in proteomics have demonstrated the substantial role of regulatory processes that occur during translational and post-transcriptional modifications to control the steady-state protein abundance, and cell type- and time-dependent expression patterns. The major factors for Pe were summarized, and it was found that the functional protein quantities, within and across tissues, are regulated by a series of events carried out by Pe at post-translation.[18,19] A large human T catalogue, which includes proteins and peptides encoded by 17,294 genes, account for approximately 84% of the total annotated protein-coding genes in humans. This is available as an interactive web-based resource at www.humanproteomemap.org.[20] The Cancer Genome Atlas (TCGA) is a large P and G database for the integrated proteogenomic analysis of the functional context to interpret genomic abnormalities, and provides a new paradigm for understanding cancer biology.[21]

## The GTP core frequently varies according to the regulation of the new environment based on the triple W and signal basin in spatiotemporal cell biology

The previous publications of the investigators discussed that for the process, from DNA to functional proteins, the G-T-P must be precisely controlled based on the "triple W" and "signal basins" in spatiotemporal cell biology.[1–3]

When and where should the gene locus be selected for transcription based on the "triple W" and "signal basins"? This can be envisaged through the recently developed database, the Human Protein Atlas.[15] In order to meet the needs of the body, signal interaction with intracellular targets take place at the right time and in the right place. This precise timescale can be observed in each cell cycle step, and even in various types of molecular interactions.[22,23] The gene expression, especially developmental gene expression, must follow the temporal regulation of the triple W. The experimental results for ecdysone-induced transcription factor E93 in controlling the development of the *Drosophila* wing provided a model, in which the extrinsic signal triggered an intrinsic transcription factor cascade that drove the development forward in time through the regulation of chromatin accessibility.[24] DNA methylation is the major approach for the epigenetic regulation of the GTP core. The advances in studies on the methylation of 5-methylcytosine (5mC) suggested that this methylation functions in novel biological contexts, such as learning and memory, or aging, based on temporal and spatial controls.[25] mRNA localization is an important step to control the protein expression. Based on temporal and spatial designation, recent researches have furthered our understanding of how individual cells spatially and temporally organize the protein synthesis through the prior localization of mRNAs.[26,27] A spatiotemporal study on immunoglobulin gene transcriptional control revealed that this process is modulated with the exact selection of target B cells and the time scale.[28] Based on the description above, the present schematic understanding of the controls of the GTP core in spatiotemporal cell biology is further presented in Figure 2b.

When should G be transcripted? Where should T (mRNAs) be localized? Which cell's P is different? Figure 2b presents our primary understanding of GTP core regulation based on the triple W in spatiotemporal cell biology. However, the conclusions probably remain imperfect. It is hoped that this could be further reformulated and validated through further discussion and exploration of this area by other researchers worldwide.

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## Conflict of interest

The authors have no conflict of interests related to this publication.

## Author contributions

HY discussed and concluded the GTP core with the corresponding author, and wrote the primary manuscript; CSN and XL collected and analyzed the data; DW revised the English text of the manuscript; HYC pointed out the topic and handled the work, revised the manuscript, and drew the figures. All authors made a significant contribution to the study, and approved the final manuscript.

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