FEBS Letters 586 (2012) 2955–2965

FEBS Letters

journal homepage: www.FEBSLetters.org

Review

Systems biology of cellular rhythms

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ARTICLE INFO

Article history:
Received 12 July 2012
Revised 17 July 2012
Accepted 17 July 2012
Available online 25 July 2012

Edited by Miguel De la Rosa, Felix Wieland and Wilhelm Just

Keywords:
Biological rhythm
Circadian clock
Cell cycle
Glycolytic and cAMP oscillations
Segmentation clock
Calcium oscillations
Oscillation in p53 and NF-κB

ABSTRACT

Rhythms abound in biological systems, particularly at the cellular level where they originate from the feedback loops present in regulatory networks. Cellular rhythms can be investigated both by experimental and modeling approaches, and thus represent a prototypic field of research for systems biology. They have also become a major topic in synthetic biology. We review advances in the study of cellular rhythms of biochemical rather than electrical origin by considering a variety of oscillatory processes such as Ca^{++} oscillations, circadian rhythms, the segmentation clock, oscillations in p53 and NF-κB, synthetic oscillators, and the oscillatory dynamics of cyclin-dependent kinases driving the cell cycle. Finally we discuss the coupling between cellular rhythms and their robustness with respect to molecular noise.

1. The unfolding of cellular rhythms

Oscillatory behavior represents one of the most conspicuous properties of life [1–3]. Periodic processes indeed underlie a variety of key physiological functions such as the sleep–wake cycle controlled by circadian rhythms, heart beating, brain rhythmic activity, respiration, hormone pulsatile secretion, and ovulation, to mention but a few. A large number of biological rhythms originate at the cellular level. The main reason why rhythmic behavior is so frequently encountered is related to the existence of feedback processes, which control the dynamics of organisms at the cellular and supracellular levels. Oscillations are clearly a systemic property, associated with regulatory interactions between the constitutive elements of biological systems, which may range from metabolic and genetic networks to cell and animal populations. Rhythmic phenomena therefore represent a prototypic field of research in systems biology. In line with the development of systems biology, rhythms have been approached, from the very beginning, both from an experimental and a modeling perspective [1,2].

Before examining in more detail the mechanism of cellular rhythms in the light of systems biology, it is useful to briefly sketch the chronological development of the field which, starting from dissociated observations, is converging to a view that unifies oscillations observed in a variety of contexts at the cellular level, in spite of the differences in period and underlying molecular mechanism. If we look at the progress of research on the molecular mechanism of cellular rhythms, it is convenient to consider its unfolding decade by decade, by listing major developments. Rhythms in the electrical activity of muscles and neurons are known experimentally for more than one hundred years, but the development of studies on their ionic mechanism dates back to the 1950s. Despite the importance of cellular rhythms of electrical nature, the present review will focus on cellular rhythms that are not electrical and originate from cellular regulations other than those that pertain to the control of voltage-gated ion channels.

An important example of cellular rhythm discovered in the 1960s was that of glycolytic oscillations which occur in yeast cells and extracts [4], and were later observed in pancreatic β cells [5]. These oscillations originate from the regulation of key glycolytic enzymes such as phosphofructokinase [1,4–7]. The next decade saw the discovery, around 1975, of oscillations of cyclic AMP (cAMP), which underlie the wavelike aggregation of *Dictyostelium* amoebae after starvation [8]. From mid-1980s to the 1990s, oscillations of intracellular Ca^{++}, and later intracellular and intercellular Ca^{++} waves, were observed in a variety of cell types, either spontaneously or upon stimulation by hormones or neurotransmitters [9,10]. Many hormones were found to be encoded in terms of the frequency of their pulsatile secretion, as exemplified by the case of gonadotropin-releasing hormone (GnRH) released by the hypothalamus as a pulse once every hour [11]. Although they have been studied for centuries and entered the field of genetic studies some four decades ago [12],

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0014-5793
http://dx.doi.org/10.1016/j.febslet.2012.07.041

the molecular bases of circadian rhythms started to be uncovered in the 1990s [13]. At the same time, progress was made on the characterization of the mitotic oscillator that drives early cell cycles in amphibian embryos and the yeast cell cycle [14].

With the rapid development of systems biology a flurry of advances were made in the following decade. First, the segmentation clock that governs somite formation in vertebrate embryos was characterized [15,16], and new oscillatory systems such as those involving the synthesis or activation of p53 [17] and NF-κB [18,19] were discovered. Finally, with the study published in 2000 of the *Repressilator* —a system of three repressors coupled cyclically [20] —the field of cellular rhythms entered a new era with the synthesis of new, artificial oscillatory networks. In this review we examine in some detail these developments. We focus preferentially on recent publications, including those that present modeling studies closely related to the experiments. Other surveys of cellular rhythms can be consulted for additional references [1–3,21–23].

2. Circadian clocks

2.1. Circadian clock mechanisms based on transcriptional regulation

Circadian oscillations represent the prototype of biological clock. They occur spontaneously, with a period of about 24 h, in all eukaryotes and certain prokaryotes such as cyanobacteria. Several recent reviews have summarized the rich flow of information collected during the last two decades in experiments on the regulatory network that controls circadian rhythms in *Drosophila*, *Neurospora*, plants, cyanobacteria, and mammals [24–28]. This network involves a dozen of genes, which may differ according to the organism. The mechanism of circadian rhythmicity is based on transcriptional regulation involving the interplay of positive and negative feedback loops [13,25–28]. Models based on transcriptional regulation have been proposed for circadian rhythms in these various organisms [29–33]. The models show that rhythmic behavior occurs in precise conditions, beyond critical values of control parameters. In the concentration space these sustained oscillations correspond to the evolution to a closed curve, known as a limit cycle. This type of oscillations—also encountered for glycolytic and Ca^{++} oscillations as well as for most other examples of rhythms discussed here—is particularly robust as the same limit cycle, characterized by its period and amplitude, is reached regardless of initial conditions [1–3,21]. Models are helpful in assessing the effect of parameter changes on oscillatory dynamics and can thus be used to predict the effect of specific mutations.

Light controls circadian rhythms in ways that differ according to the organism. Thus, in *Drosophila*, the rate of degradation of TIM, a clock protein, increases in the light phase. In mammals, light enhances the expression of *Per* genes, which play a key role in the indirect negative feedback that lies at the core of the circadian oscillatory mechanism. Phase shifts induced by light pulses as well as the entrainment of the oscillations by light–dark cycles can be modeled through modulation of light-controlled parameters. Such simulations help to understand the nature of phase response curves, to identify the conditions in which entrainment occurs, and to clarify the dynamics of resynchronization after jet lags. The circadian pacemaker in mammals is located in the suprachiasmatic nuclei (SCN) within the hypothalamus, but circadian clocks operate in a number of peripheral tissues [26,34].

2.2. Non-transcriptional regulatory mechanisms: Kai phosphorylation and peroxiredoxins

In some organisms, e.g., cyanobacteria, circadian rhythms may also originate from a non-transcriptional regulatory mechanism. Thus, in *Synechococcus*, as shown in vitro [35,36], the mechanism responsible for circadian oscillations relies on multiple phosphorylation of the KaiC protein. Several models have been proposed for this rhythmic phenomenon [37–39]. The Kai oscillator is coupled to a mechanism based on transcriptional regulation [40]. Another instance of non-transcriptional origin of circadian behavior has recently been reported for the microalga *Ostreococcus tauri* [41] and for human erythrocytes [42] where circadian oscillations are linked to oxidation–reduction cycles of peroxiredoxins. The latter mechanism has recently been shown to coexist in many cell types with the mechanism based on transcription–translation feedback loops discussed in Section 2.1. As it preceded the appearance of the latter mechanism in the course of evolution, it represents the oldest circadian oscillatory mechanism identified so far at the cellular level [43]. A challenging question pertains to the molecular mechanism of the peroxiredoxin oscillator that remains to be fully characterized and modeled theoretically.

2.3. Physiological impact of the circadian clock

Circadian clocks control metabolism [44,45] and a wide variety of physiological functions, such as the sleep–wake cycle. Among the most remarkable findings is the observation of a clinical symptom, the familial advanced sleep phase syndrome (FASPS), which is associated with a mutation affecting *hPer2*, a gene of the human circadian clock [46]. A decrease in the phosphorylation of the PER2 protein is accompanied by a decrease in the intrinsic period of the circadian clock [47], which corresponds to a phase advance of the sleep–wake cycle of several hours upon entrainment by the light–dark cycle (people affected by the syndrome go to sleep around 7:30 pm and awake around 4:30 am). The link between the decrease in PER phosphorylation and the phase advance of the circadian clock has been modeled theoretically [30]. Models also bring to light the possibility of other disorders related to the lack of entrainment of the circadian clock, a condition known as the non-24 h sleep–wake cycle syndrome, which affects blind people but may also occur in sighted people [48]. The model predicts that this phenomenon is favored when the levels of some key clock proteins are not properly balanced.

Beyond their physiological impact, also manifested by the jet lag that follows changes in the phase of the light–dark cycle associated with long-distance flights, circadian rhythms have marked effects on the action of drugs. Thus, pharmacological dose-response curves depend on the time of the day at which they are established. That the action of drugs often varies according to the time of their administration stems from the fact that many enzyme activities display circadian variations. Circadian rhythms therefore possess important therapeutic implications, which have been explored, in particular, for the chronopharmacology of anticancer drugs [49]. A case in point is that of 5-fluorouracil (5-FU), used in the treatment against colon cancer, which kills cells in the S phase of DNA replication. Animal and clinical studies show that the administration of 5-FU following a circadian pattern peaking at 4 am is more efficient and better tolerated than a similar pattern peaking at 4 pm or constant 5-FU delivery. A modeling study suggests [50] that the circadian variation in drug efficacy is related to the fact that the fraction of cells in S phase itself oscillates with a defined phase with respect to the circadian clock.

3. Frequency-encoded cellular rhythms

3.1. Cyclic AMP oscillations in Dictyostelium cells

After starvation, *Dictyostelium discoideum* amoebae aggregate by a chemotactic response to cAMP pulses secreted with a

periodicity of about 5 min by cells that behave as aggregation centers [8,51]. The oscillations are due to the regulation of cAMP synthesis, which, in this species of slime mold, is subjected to mixed positive and negative feedback of extracellular as well as intracellular nature. Thus, cAMP secreted into the extracellular medium binds to a plasma membrane receptor and thereby activates the synthesis of intracellular cAMP by adenylate cyclase. This positive feedback loop is limited by negative feedback based on cAMP-induced receptor desensitization [52]. An intracellular negative feedback loop based on PKA-mediated inhibition of cAMP accumulation provides an additional source of oscillatory behavior [53].

The pulsatile signals of cAMP are encoded in terms of their frequency: only signals delivered at the physiological frequency of one pulse every 5 min are capable of inducing aggregation and cell differentiation after starvation [54]. The mechanism of frequency encoding of cAMP oscillations relies on receptor desensitization; if the interval between successive pulses is too brief, the receptor has not enough time to fully resensitize and the response in the form of cAMP synthesis will be reduced [1,52]. A similar frequency encoding of the pulsatile signal is observed for secretion of the hormone GnRH in mammals: only when delivered by the hypothalamus at the physiological frequency of one brief pulse per hour does GnRH support the establishment of levels of the gonadotropic hormones LH and FSH appropriate for inducing ovulation [55]. The existence of an optimal frequency of pulsatile signaling has been predicted theoretically both for cAMP pulses in *Dictyostelium* and for the pulsatile secretion of GnRH [56]. As for cAMP oscillations in *Dictyostelium* [52], the mechanism for pulsatile GnRH secretion has been modeled in terms of self-amplification of GnRH release upon binding of GnRH to its membrane receptor [57].

3.2. Cytosolic Ca^{++} oscillations

By their ubiquity and the significance of their physiological functions, oscillations in cytosolic Ca^{++} represent one of the most important examples of cellular rhythm; depending on cell type, their period ranges from seconds to minutes [9,10]. These oscillations result from the complex interplay of activatory and inhibitory processes that regulate both Ca^{++} release from the endoplasmic reticulum (ER) and Ca^{++} entry from the extracellular medium. Release from the intracellular stores is brought about by an increase in the concentration of inositol 1,4,5-trisphosphate (IP_3), the messenger synthesized in response to hormonal stimulation. IP_3 receptors are located in the membrane of the ER and release Ca^{++} upon ligand binding. As this receptor is activated and inhibited by Ca^{++} itself, oscillations can develop [9]. In most cell types, this self-sustained release of Ca^{++} from intracellular stores is accompanied by an increased influx of Ca^{++} across the plasma membrane.

Oscillations in cytosolic Ca^{++} are involved in the control of gene expression and cell differentiation [9,10,58], in secretory processes [59,60] and in triggering intestinal or uterine contractions [61,62], to quote but a few examples. A key feature of Ca^{++} oscillations is that they are encoded in terms of their frequency [9,10,63], much as cAMP oscillations in *Dictyostelium* and GnRH pulses. One way of encoding Ca^{++} spikes by their frequency is through the control of Calmodulin kinase II (CaMKII) [64]. This process has been modeled theoretically [65].

3.3. Oscillations of p53

Since the crossed regulatory interactions between the tumor suppressor p53 and its inhibitor Mdm2 were predicted to give rise to oscillations [17], numerous experimental [66–68] and theoretical [69,70] studies have been devoted to the mechanism of p53 oscillations and to their role in the response to DNA damage. The dynamics of p53 pulses, which occur with a periodicity of a few hours, have been determined in single cells as well as in cell populations. As in the other instances where the dynamic pattern of the signal rather than its sole level carries information, the temporal profile of p53 has been shown to govern cellular response [71,72]. Thus, when cells are manipulated to produce a sustained p53 level instead of p53 pulses in response to DNA damage, the constant level of p53 elicits the expression of a different set of genes and also alters cell fate. Indeed, cells subjected to p53 pulses recover from DNA damage, whereas cells exposed to sustained p53 signaling undergo senescence [72].

3.4. Oscillations of NF-κB

A similar situation is encountered for the transcription factor NF-κB, which plays a key role in inflammation. Since the discovery of NF-κB oscillations of a period of the order of 100 min, several mathematical models have been proposed for the phenomenon [18,19,73,74]. The mechanism of oscillations in NF-κB triggered by TNFα stimulation involves the regulatory interactions with its inhibitor I-κB: when NF-κB is released from I-κB in the cytosol, it is translocated into the nucleus. The regulation by NF-κB of I-κB transcription represents a delayed negative feedback loop that drives oscillations in NF-κB translocation. Here again the temporal profile of NF-κB controls the cellular response: the timing and specificity of NF-κB-dependent transcription are governed by the frequency of TNFα pulses [75].

3.5. Nucleocytoplasmic oscillations of transcription factors

On a shorter time scale oscillations in nucleocytoplasmic shuttling of transcription factors have been observed in yeast. Thus, in yeast cells subjected to stress, the factor Msn2 shows coordinated movements in and out of the nucleus with a period of the order of 6 min [76,77]. Experimental evidence supported by a modeling approach indicates that the phenomenon originates from periodic activation of Msn2 by PKA, driven by cAMP oscillations [78] that are reminiscent of those observed due to a similar mechanism in *Dictyostelium* cells [53]. Periodic nuclear translocation, playing a role in gene regulation, has been observed in yeast for another transcription factor, Crz1 [79]. Oscillatory translocation of transcription factors to the nucleus results in their periodic activation and could thereby govern the frequency-dependent expression of specific groups of genes [80].

4. The cell cycle as self-sustained oscillator

4.1. The embryonic and yeast cell cycles

Experimental progress on the mechanism of the cell division cycle was first made on early cell cycles in amphibian embryos, which are driven by the periodic activation of a *mitosis promoting factor*, MPF, that was shown to be a complex between a cyclin protein and a kinase, Cdc2 [14]. These cell cycles occur with a period of 30 min, and are driven by cyclin synthesis [81]. The kinase Cdc2 is activated through dephosphorylation by phosphatase Cdc25 once the cyclin level exceeds a threshold. The periodicity of MPF activation relies on a negative feedback loop, as Cdc2 activation leads to cyclin degradation [82]. Early models for the embryonic cell cycles showed that sustained oscillations indeed occur as a result of such negative auto-regulation in a phosphorylation–dephosphorylation cascade [83]. Positive feedback also occurs in this system, because the kinase Cdc2 activates phosphatase Cdc25 and inhibits its inhibitory kinase Wee1. Models incorporating such positive feedback loops were proposed by Novak and Tyson [84] for the embryonic

cell cycles. They stressed the role of positive feedback in allowing for the coexistence between two distinct, stable levels of activity of Cdc2, a phenomenon known as *bistability*. Experimental studies based on theoretical models demonstrated in frog egg extracts the occurrence of bistability and of the associated phenomenon of hysteresis in which Cdc2 periodically undergoes abrupt transitions between a low and a high state of activity, driven by variations in the level of cyclin due to alternating phases of accumulation and Cdc2-induced degradation [85,86].

Yeast was the other organism of choice for which major advances were made on characterizing the biochemical mechanisms governing the transitions between the successive phases of the cell cycle [14]. The dynamics of the yeast cell cycle in terms of cyclin-dependent kinase (Cdk) regulation through kinases and phosphatases continue to be the topic of numerous experimental studies [87–89]. A comprehensive computational model for the ordering of cell cycle events in budding yeast under control of cell mass accounts for the phenotype of a large number of cell cycle mutants [90].

4.2. Temporal self-organization of the Cdk network driving the mammalian cell cycle

In mammals a network of cyclin-dependent kinases controls the transitions between the successive phases G1, S (DNA replication), G2 and M (mitosis) of the cell cycle (see Fig. 1). The Cdks are controlled through phosphorylation–dephosphorylation, through cyclin synthesis and degradation, and also through association with protein inhibitors such as p21 [91]. Models have been proposed for parts of the cell cycle, particularly the G1/S transition [92–94]. A more detailed model for the Cdk network accounts for several properties of the mammalian cell cycle [95]. The model contains four modules, each centered around one cyclin/Cdk complex. The cyclin D/Cdk4-6 and cyclin E/Cdk2 complexes promote progression in G1 and elicit the G1/S transition, respectively; the cyclin A/Cdk2 complex ensures progression in S and the transition S/G2, while the activity of the cyclin B/Cdk1 complex brings about the G2/M transition (Cdk1 is the homolog of the kinase Cdc2). This 39-variable model shows that in the presence of sufficient amounts of growth factor the Cdk network is capable of temporal self-organization in the form of sustained oscillations. The transition from cell quiescence to cell proliferation can be viewed as the switch from a stable to an unstable steady state of the Cdk network [95]. Beyond this critical point of instability, instead of reaching a stable steady level in the course of time, the various cyclin/Cdk complexes undergo sustained oscillations (Fig. 2A), which correspond to the ordered, sequential activation of the various cyclin/Cdk complexes that control the successive phases of the cell cycle. The regulatory structure of the Cdk network is such that each Cdk module is activated in turn in a transient manner: once a module is activated, it triggers the activation of the next Cdk module and inhibits the previous modules in the network. The model accounts for the antagonistic effects of E2F and pRB, which respectively promote and hinder cell cycle progression. It shows that there are multiple ways to induce the transition from quiescence to proliferation. Such a transition may originate, for example, from the overexpression of oncogenes or from the decrease in activity of tumor suppressors such as pRB [95].

Less complex models that retain the core regulatory structure of the Cdk network show a similar capability of temporal self-organization in the form of sustained oscillations [96]. Experimental and modeling studies have emphasized the role of positive feedback in rendering cell cycle transitions irreversible [97]. Reduced models for the Cdk network allow to analyze in further detail the role of positive feedback loops involving Cdk1 and Cdk2 [98]. Increasing the number of these positive feedback loops not only ensures redundancy but also strengthens the robustness of Cdk oscillations (see below, Section 7). This holds with the observation that MPF oscillations in frog egg extracts become damped in the absence of positive feedback on Cdc2 [99].

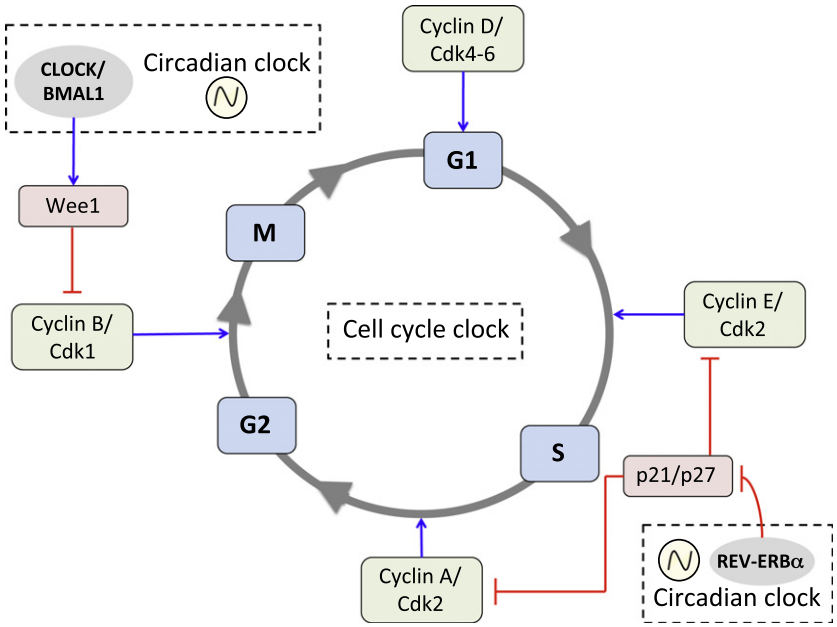

Fig. 1. Coupled cellular clocks. The mammalian cell cycle is controlled by a family of cyclin-dependent kinases: cyclin D/Cdk4-6 and cyclin E/Cdk2 promote progression in G1 and elicit the G1/S transition, cyclin A/Cdk2 ensures progression in S and G2, while the peak of cyclin B/Cdk1 brings about the G2/M transition. The activity of cyclin/Cdk complexes is regulated by Cdk inhibitors such as p21/p27. At the G2/M transition, the kinase Wee1 inhibits Cdk1 by phosphorylation. The circadian clock can regulate progression in the cell cycle in multiple ways. Indeed, the circadian clock complex CLOCK/BMAL1 induces expression of Wee1, while another circadian clock complex, REV-ERBα, represses the synthesis of the Cdk inhibitor p21/p27.

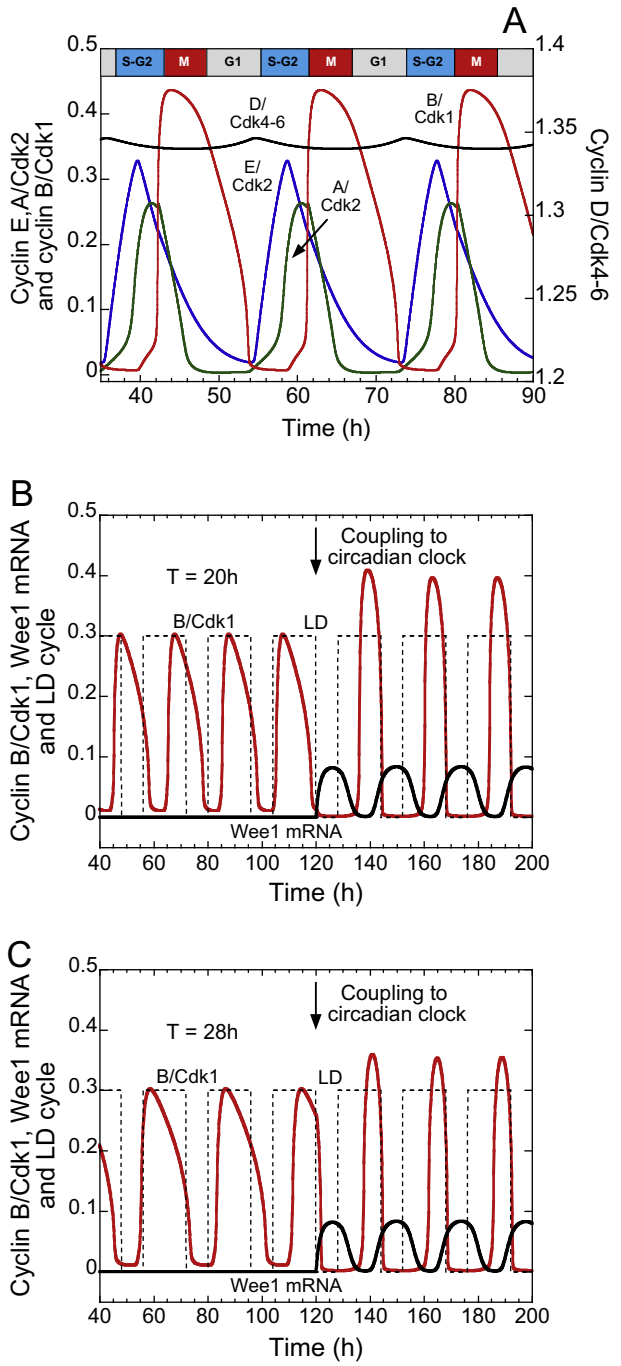

Fig. 2. Sustained oscillations of the Cdk network and entrainment of the cell cycle by the circadian clock. A detailed model predicts that the Cdk network driving the cell cycle is capable of temporal self-organization in the form of sustained oscillations of the different cyclin/Cdk complexes (A): cyclin D/Cdk4-6 (in black), cyclin E/Cdk2 (in blue), cyclin A/Cdk2 (in green), and cyclin B/Cdk1 (in red) [95]. The oscillations correspond to the repetitive, transient activation of the various cyclin/Cdk complexes, which promote progression in the successive phases of the cell cycle. Entrainment of the cell cycle by the circadian clock through the kinase Wee1 in the same model is shown in (B) and (C). The curves give the time evolution of cyclin B/Cdk1 (in red) and Wee1 mRNA (in black) in the absence (for t<120 h) or presence (for t > 120 h) of coupling to the circadian clock when the autonomous period of the cell cycle is equal to 20 h (B) or 28 h (C). In both cases the cell cycle is entrained to a circadian period when the synthesis of the kinase Wee1 is controlled by the circadian complex CLOCK/BMAL1 [136]. The dashed line in (B) and (C) denotes the light-dark (LD) cycle.

5. Cellular oscillators in development

5.1. Periodic cellular aggregation

Several oscillations illustrate the role of cellular rhythms in development. A classical example is provided by the wavelike patterns of aggregating cells observed in *Dictyostelium* after starvation with a period of 5 to 10 min. These waves of cellular movement are superimposed on concentric or spiral waves of cAMP, which originate from the oscillatory synthesis of cAMP (see Section 3.1) coupled with its diffusion in the extracellular medium [51,100,101]. Another example is the swarming behavior of myxobacteria. In *Myxococcus xanthus*, a biochemical oscillator involving proteins of the Frz family governs changes in the polarity of cell movement, with a period of about 8 min, which result in the formation of a multicellular structure [102]. The oscillatory mechanism has been modeled in terms of a negative feedback loop in a phosphorylation cascade involving the Frz proteins [103]. Accompanying the reversals in cell movement, an Frz protein moves in an oscillatory pattern between the cell poles [104]. A physiologically distinct, but somewhat related phenomenon is encountered in *Escherichia coli* where rapid pole-to-pole oscillations of the Min proteins with a period of about 100 s ensure that division is restricted to the middle of the cell [105].

5.2. The segmentation clock

One of the most remarkable developments of the last 15 years in the field of cellular rhythms pertains to the segmentation clock that controls the periodic formation of somites in vertebrate embryos. This clock controls the oscillatory expression of specific genes involved in somitogenesis with a period of the order of 30 min in zebrafish to 1.5–2 h in mouse and chicken embryos [106–108]. Because the clock results in the formation of a spatial pattern, this oscillatory system provides an exquisite example of spatiotemporal organization at the supracellular level [16,108]. The existence of a clock was predicted by the analysis of a theoretical model [109] and subsequently confirmed experimentally [15].

The Notch, FGF and Wnt signaling pathways are involved in the mechanism of the segmentation clock [107,110,111]. Oscillations in gene expression with specific phase relationships have been demonstrated in these three pathways. A model for this cellular rhythm based on the cross-talk between the three oscillatory signaling pathways has been proposed; in each pathway oscillations would result from negative feedback based on another type of molecular implementation [112]. This model for temporal oscillations was later extended and incorporated into a model for somitogenesis [113]. The possibility nevertheless remains that a yet to be discovered pacemaker mechanism drives oscillations in the FGF, Notch and Wnt pathways and thereby controls the segmentation clock [110,114].

Other cellular oscillations related to those observed in the segmentation clock have been characterized. Thus, oscillations in the expression of genes of the Notch signaling pathway, such as *Hes1*, have been observed in cell cultures. These oscillations are based on negative feedback on transcription [115]. They have been modeled in terms of a negative feedback loop incorporating a delay [116], as proposed for the segmentation clock in zebrafish [117] and, more generally, for oscillations in the expression of Hes 1, p53 and NF-κB [118].

6. Coupled cellular clocks

6.1. Intercellular coupling

Cells displaying a given cellular rhythm can synchronize through intercellular communication as exemplified by the case of circadian rhythms (see Section 2). Circadian oscillations already occur in isolated SCN neurons; the intercellular coupling that results in their synchronization [119] has been modeled theoretically [120,121]. Another example of intercellular coupling is provided by the synchronization of glycolytic oscillations in yeast cell populations [122,123]. Intercellular coupling of oscillating cells allows for propagation of cAMP waves in *Dictyosteliium* [51] and of Ca^{++} waves in a variety of cell types such as endothelial cells [124] or hepatocytes [125]. In zebrafish, intercellular communication through the Delta–Notch signaling system participates in the mechanism of the segmentation clock [117].

6.2. Coupling oscillatory circuits within clock networks

Within a cell, distinct rhythms, or even distinct oscillatory circuits within a given clock network, may be coupled. We already encountered an example of such coupling. Thus, in the segmentation clock (see Section 5.2), oscillations occur in the FGF, Wnt and Notch signaling pathways [107,110,111] and could synchronize as a result of cross-talk between these three pathways [112] (an alternative possibility is that the three pathways are controlled by a still uncharacterized common master oscillator [110,114]). Another example is provided by the cell cycle driven by the Cdk network. In view of its complexity (see Fig. 1), it is not surprising that the Cdk network contains several circuits that are capable, each on its own, to produce oscillations [95,96]. Because of their tight coupling through regulatory interactions, these oscillators are synchronized so that one peak of cyclin B/Cdk1 generally occurs per peak of cyclin E/Cdk2 and cyclin A/Cdk2 over one cell cycle. If the coupling between the oscillatory circuits weakens, however, internal synchronization may break down, leading, for example, to several peaks of Cdk2 per peak of Cdk1. Such a situation corresponds to endoreplication in which multiple rounds of DNA replication occur in the absence of mitosis [126]. The phenomenon is observed in models for the yeast [127] and mammalian cell cycles [95,96]. Additional experimental evidence for multiple oscillatory circuits linked to the cell cycle has been obtained [128,129].

6.3. Cell cycle entrainment by the circadian clock

Different cellular clocks may also be coupled. A most striking example is provided by the coupling of the cell cycle to the circadian clock, which has long been investigated in unicellular organisms [130–132]. In mammalian cells a first mode of coupling occurs through control of the expression of the cell cycle kinase Wee1, a Cdk inhibitor, by the circadian clock protein BMAL1 [133]. Additional modes of coupling are mediated through circadian control of cyclin E and the Cdk inhibitor p21 [134,135]. When incorporating these modes of coupling, the model for the mammalian cell cycle [95] shows that entrainment by the circadian clock can occur over a large domain of intrinsic period of the cell cycle [136].

The phenomenon of entrainment of the cell cycle by the circadian clock via Wee1 is illustrated in Fig. 2 for the case where the intrinsic period of the cell cycle prior to coupling is 20 h (B) or 28 h (C). In both cases, the coupling readily results in a shift of the cell cycle period to the 24 h period of the circadian clock; the latter is itself entrained to the light–dark cycle represented as a square wave (dashed line). The question arises as to how the circadian variation of a Cdk inhibitor such as Wee1 is capable of accelerating the cell cycle and bringing its period down from 28 h to 24 h ? Numerical simulations of the model for the Cdk network indicate that this paradoxical, counterintuitive effect is made possible by a reduction in the width of the activity peaks of the various cyclin-dependent kinases (Fig. 2C) [136].

6.4. Calcium oscillations mediate resumption of the cell cycle at fertilization

Oscillations in cytosolic Ca^{++} triggered at fertilization provide the example of another cellular rhythm capable of controlling the cell cycle clock. Upon fertilizing an egg, the spermatozoon injects into it a protein identified as phospholipase C zeta [137], which raises the level of cytosolic Ca^{++} by inducing its release from intracellular stores. A self-amplified regulatory process based on CICR (Ca^{++}-induced Ca^{++} release) triggers sustained oscillations of Ca^{++} [63], which induce resumption of the cell cycle [138]. Prior to fertilization, the cell cycle was indeed blocked in the metaphase of the second meiosis by the cytostatic factor (CSF) that prevented degradation of cyclin B. How do Ca^{++} oscillations lead to the resumption of cell cycling? Activation of CaMKII by Ca^{++} spiking leads to hydrolysis of CSF and thereby allows resumption of the cell cycle (see scheme in Fig. 3). Such a cascade uncovered by experimental work [138] has been modeled theoretically [139]; the model permits to clarify the role of Ca^{++} oscillations in triggering the onset of cell cycling. These observations have recently led to clinical applications. A case of male infertility has been described in which the disorder originates from the absence of Ca^{++} oscillations as a result of decreased activity of phospholipase C zeta in sperm; in this pathology, appropriate pulses of ionophore applied during the procedure of intracytoplasmic sperm injection can result in egg activation [140].

6.5. Multiple rhythms are coupled in pancreatic β cells

In certain cells, several rhythms of different periods originating from mechanisms based on distinct modes of cell regulation may coexist. A case in point is that of pancreatic β cells in which membrane potential bursting oscillations as well as glycolytic and Ca^{++} oscillations with periods of several minutes have been observed in relation to pulsatile insulin release [5,141,142]. These cells are further controlled by the circadian clock [143], which coordinates insulin secretion with the sleep–wake cycle; ablation of the pancreatic circadian clock can trigger onset of diabetes mellitus [144]. How these closely intertwined rhythms cooperate at the cellular level, and at the intercellular level within and between different islets of Langerhans, to produce coherent pulsatile insulin release remains to be fully established.

7. The new era of synthetic oscillators

In 2000 the construction of the first synthetic oscillator signaled the entry into the new era of artificial cellular rhythms. This oscillator, known as the Repressilator, expressed in *E. coli*, consists of a set of three repressors coupled cyclically [20]. Such regulatory structure is reminiscent of recurrent cyclic inhibition, which was shown to produce sustained oscillations in neural networks [145]. This first success was followed by the development of a variety of synthetic oscillatory networks expressed in bacteria or mammalian cells, mostly based on genetic regulation. These synthetic networks display oscillations with tunable frequencies covering a wide range, from tens of minutes up to 24 h [146–150]. All these synthetic oscillators are based on one form or another of negative feedback, the realization of which is often highly sophisticated. Coupling the oscillatory network to a mechanism

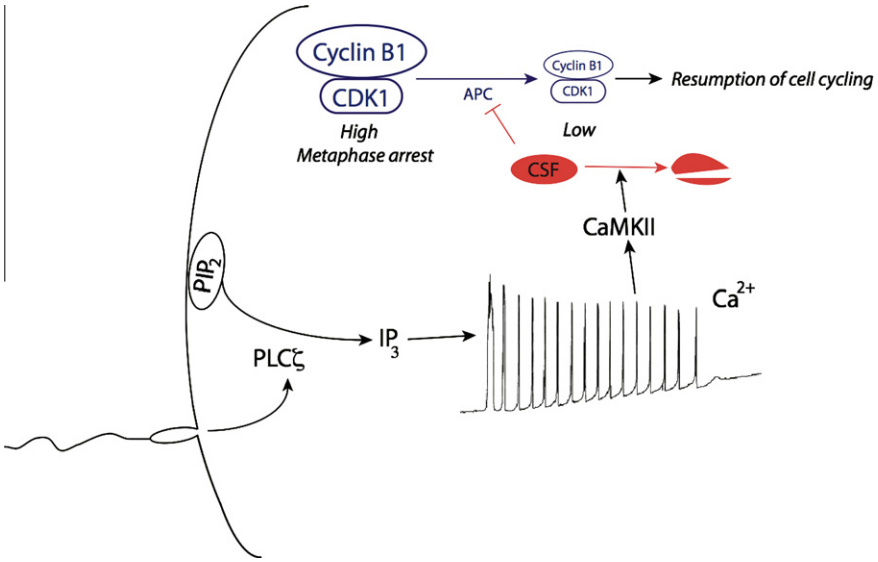

Fig. 3. Ca^{++} oscillations control the resumption of cell cycling after egg fertilization. Upon fertilizing the egg a spermatozoon injects an enzyme, phospholipase C zeta (PLC ζ), which synthesizes inositol trisphosphate and thereby elicits a rise in cytosolic Ca^{++}. Through a mechanism involving Ca^{++}-induced Ca^{++} release, this results in sustained Ca^{++} oscillations, which lead to the activation of CaMKII. The latter enzyme eventually brings about the degradation of the cytostatic factor (CSF) which blocks the cell cycle by preventing the degradation of cyclin B. Removal of the CSF block allows resumption of cell cycling.

of quorum sensing allows the synchronization of oscillations in bacterial populations, which can take the form of propagating waves [151,152].

The interest of synthetic oscillators is that they allow to finely tune the parameters that control the oscillatory dynamics of the regulatory network. This contributes to a detailed understanding of the conditions in which periodic behavior arises in biological systems. Such endeavor could be facilitated by the construction of synthetic oscillators uncoupled from natural cellular rhythms, while the latter are often intertwined. Furthermore, the development of artificial cellular oscillators opens the way to pharmacological applications such as pulsatile drug delivery.

8. Robustness of cellular rhythms with respect to molecular noise

Oscillations observed in single cells are often noisy [20,153]. The question arises of how a global, coherent temporal organization may originate from such fluctuating oscillatory variations at the cellular level. This question was initially raised in respect to circadian rhythms. Barkai and Leibler pointed out [154] that cellular levels of protein or mRNA molecules can sometimes be reduced, which may jeopardize conclusions based on deterministic models. In such cases it becomes necessary to resort to stochastic simulations. Such simulations show that deterministic models provide good approximations for the behavior observed in stochastic ones, as soon as a hundred or more molecules are present in the oscillatory mechanism [155,156]. This conclusion holds not only for periodic but also for chaotic behavior [157].

Stochastic versions have been studied for many models proposed for cellular rhythms and account, for example, for the irregular dynamics of nucleocytoplasmic oscillations of the transcription factor Msn2 in yeast cells [158]. Fluctuations play a particularly significant role in the case of Ca^{++} signaling, since local fluctuations amplified by Ca^{++}-induced Ca^{++} release are often at the origin of Ca^{++} puffs which may transform into Ca^{++} waves [159,160]. Stochastic simulations of circadian rhythms show that the robustness of circadian rhythms with respect to molecular noise is enhanced in the presence of positive feedback loops, which give rise to bistability and the associated phenomenon of hysteresis (see Section 4.1).

The conclusion that oscillations based on hysteresis prove to be more resistant to molecular noise [154,161] is also reached in models for the Cdk network driving the mammalian cell cycle. Positive feedback loops abound in this regulatory system; their effect is to sharpen the transitions between successive phases of the cell cycle and to make them irreversible [85,86,88,97]. When viewing the cell cycle as a cellular clock, it is useful to determine the effect of positive feedback loops on the robustness of Cdk oscillations with respect to molecular noise [98]. Stochastic simulations of reduced models for the Cdk network indicate that the amplitude and regularity of Cdk oscillations increase with the number of positive feedback loops (Fig. 4). The reason for such enhanced robustness is that multiple positive feedback loops not only provide redundancy in regulation but also extend the domains of bistability as a function of control parameters [162,163], and thereby buffer Cdk oscillations with respect to molecular noise [98].

9. Concluding remarks: Feedback loops and cellular rhythms

Cells are open systems that exchange matter and energy with their environment. By doing so they generally evolve toward a stable steady state. However, once the system operates sufficiently far from equilibrium and when its kinetics acquire a nonlinear nature, the steady state may become unstable [164]. Feedback processes and cooperativity are two main sources of nonlinearity that favor the occurrence of instabilities in biological systems. When the steady state becomes unstable, the system moves away from it and may either evolve to another, stable steady state (in case of bistability) or it may undergo sustained oscillations around the unstable steady state [1,21,23,164].

In spite of the diversity in molecular mechanism, cellular rhythms share common properties [1,21,23]. They occur when a steady state becomes unstable beyond a critical value of some control parameter. The mechanism of instability that causes oscillations originates from regulatory feedback processes. Understanding the molecular mechanism of oscillations requires clarification of the chain of events that cause each variable of the

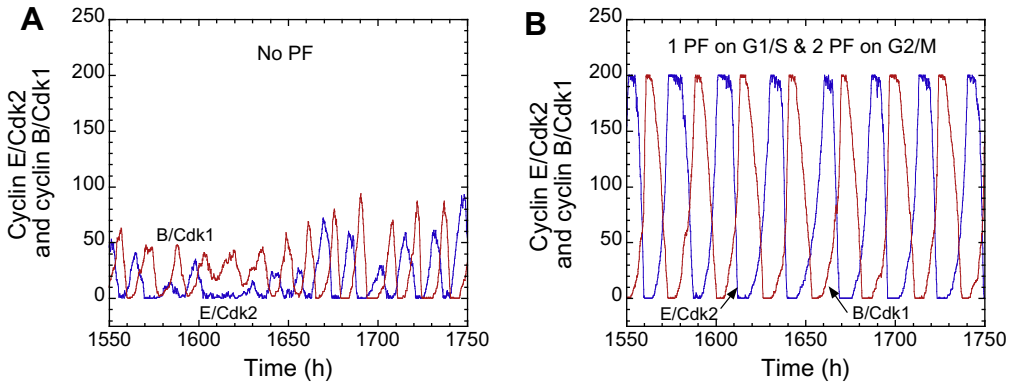

Fig. 4. Effect of positive feedback (PF) loops on the robustness of oscillations in the Cdk network driving the mammalian cell cycle. Shown is the stochastic time evolution of cyclin E/Cdk2 (in blue) and cyclin B/Cdk1 (in red) in the absence of any positive feedback loop (A) or in the presence of 3 such loops (B): A first PF originates in G1/S from the activation by cyclin B/Cdk1 of the phosphatase Cdc25 that activates Cdk1; the two PF loops in G2/M both involve cyclin B/Cdk1, which activates its activating phosphatase Cdc25 and inhibits its inhibitory kinase Wee1. The presence of positive feedback loops increases the amplitude of the cyclin/Cdk oscillations and their robustness with respect to molecular noise [98]. The curves are obtained by means of stochastic simulations for the parameter values listed in Tables 2 and 3 of Ref. [98] for the corresponding deterministic case, with $V_{1e2f} = 0.35\ h^{-1}$, $V_{1Me} = 1\ \mu M^{-1}h^{-1}$, $V_{1Ma} = 0.7\ h^{-1}$, $V_{1Mb} = 1.1\ \mu M^{-1}h^{-1}$, $V_{1cdc20} = 4\ h^{-1}$, and $K = 0.01\ \mu M$.

system to periodically rise and fall. Elucidation of this mechanism largely reduces to identifying the feedback processes that lie at the core of the oscillations. The latter may originate from positive or negative feedback, or from a mixture of both [1,21,165,166]. The interplay between a large number of variables coupled through multiple regulatory interactions makes it difficult, if not impossible, to fully grasp the dynamics of oscillatory behavior without resorting to modeling and computer simulations.

Positive feedback can give rise to bistability, and negative feedback can lead from bistability to sustained oscillations via repeated cycles of hysteresis. Even if negative feedback alone can produce sustained oscillations, the presence of positive feedback may serve to enhance the robustness of the oscillations by increasing their amplitude and by buffering them with respect to molecular noise, as exemplified by the case of oscillations in the cell cycle network (see Sections 4 and 7, and also Fig. 4).

The cellular regulations that form the core of the oscillatory mechanism may take multiple forms, and sometimes several of these cooperate to give rise to the instability that paves the way for rhythmic behavior [1,3,21]. Positive or negative feedback associated with the voltage-dependent activity of ion channels in the membrane of electrically excitable cells underlies the periodic generation of action potentials in neural and cardiac rhythms. These rhythms form a large, important class of cellular and supracellular oscillators that falls outside the scope of the present review devoted to cellular rhythms of biochemical origin. Feedback loops in the regulation of enzyme or receptor activity by allosteric transitions or by covalent modification, e.g., phosphorylation–dephosphorylation, participate in the mechanism of cyclic AMP oscillations in the slime mold *Dictyostelium discoideum*, in the mechanism of glycolytic oscillations in yeast, and in the oscillatory dynamics of the network of cyclin-dependent kinases driving the cell cycle. The regulation of gene expression, associated with mechanisms of post-translational control, forms the core of the circadian clock network, even if other mechanisms, not based on transcriptional regulation, have recently been uncovered. Regulation of transport between the cytosol and the endoplasmic reticulum or the nucleus is involved in the onset of Ca^{++} oscillations in a variety of cell types and in periodic nucleo-cytoplasmic shuttling of the transcription factor Msn2 in yeast. Finally, mechano-chemical instabilities play a role in a number of cellular rhythms involving molecular motors or the cytoskeleton [167].

Cellular rhythms possess many functions. One of these is the capability of encoding a signal in terms of its frequency rather than its amplitude. Frequency encoding of periodic signals is exemplified by the pulsatile release of hormones such as GnRH, cAMP signals in *Dictyostelium*, Ca^{++} oscillations, p53 and NF-κB (see Section 3). The temporal profile of these pulsatile signals carries information that governs the efficiency of intercellular communication or the differential expression of genes. Another function, shared by circadian or annual clocks, is to allow adaptation to the periodic nature of the environment. The cell cycle and the segmentation clock play key roles in development, while other rhythms drive the periodic operation of the heart, the respiratory system, and intestinal or uterine contractions. The sleep-wake cycle and metabolism are controlled by the circadian clock. Finally, rhythms of electrical nature underlie the periodic functioning of neurons that holds the key to consciousness as well as the rhythmic activity of central pattern generators that control movements. What would life be without rhythms?

Acknowledgments

This work was supported by grant n° 3.4607.99 from the Fonds de la Recherche Scientifique Médicale (F.R.S.M., Belgium), by the Belgian Federal Science Policy Office (IAP P6/25 "BioMaGNet": "Bioinformatics and Modeling- From Genomes to Networks"), and by the F.R.S.-FNRS (Belgium) in conjunction with the Erasys-Bio+ project C5Sys, "Circadian and Cell Cycle Clock Systems in Cancer". G.D. and J.C.L. are, respectively, Senior Research Associate and Research Associate at the F.R.S.-FNRS (Belgium). C.G. currently holds a postdoctoral fellowship from the Philippe Wiener – Maurice Anspach Foundation at the Department of Biochemistry, University of Oxford (Oxford, UK).

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