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A Theory of Cortical Neuron-Astrocyte Interaction

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A neuron-astrocyte theory, in which motile astrocytes organize and modulate synaptic activity, may permit widely divergent aspects of brain function and pathology to be viewed from a single theoretical vantage.

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With the discovery of calcium waves in astrocytes and the demonstration that calcium waves can be propagated through astrocytic networks(1, 2), another layer of complexity may have been added to associative cortical functioning. The presence of glial signaling in the brain and demonstrated interactions between neurons and glia (3, 4, 5) have served as a warning to neurotheoreticians that neuronal networks alone may not explain this biological computer. Models of associative cortical function must now account for not only the activities of astrocytes, the largest cell population in the brain, but also for the relationships astrocytes and astrocytic signaling networks have with neurons in the encoding and manipulation of sensory information. In addition to describing the mechanisms by which associative cortex processes and utilizes information, any clinically useful model should also provide insight into the maladies to which the brain is universally vulnerable. A theory fulfilling these criteria departs radically from currently held concepts of brain function and proposes that motile astrocytes control synaptic activity and organize synapses into synchronously firing groups.

Dynamic Aspects of the Neuron-Astrocyte Relationship

Astrocytes are not necessarily a stationary cell population (6, 7, 8); astroglia in vitro extend processes with highly motile tips (9) and human fetal astrocytes in tissue culture are in a state of almost constant motion (Antanitus D., unpublished observations). Additional evidence for astrocytic movement has been observed in vitro, where astrocytes change shape by developing filopodial extensions when exposed to neurotransmitter (10). The direction of filopodial growth is vectored up the concentration gradient of the applied neurotransmitter. Such observations, if applicable to the brain in situ, support the theoretical premise that the filamentous cytoplasmic extensions of astrocytes in vivo may be actively motile and neurotransmitter tropic. In addition, evidence shows that astrocytes can swell or shrink depending on activity in nearby neuronal elements (11, 12, 13); this, too, may alter the spatial relationship between the astrocyte and nearby neuronal processes, including pre- and postsynaptic elements.

In vivo, astrocytes envelop synapses so intimately that they are thought to compartmentalize the spaces between cells in associative cortex (14) (Fig. 1a). One astrocyte may envelop some of the synapses of several neurons, and one neuron may have its synapses enveloped by several astrocytes. This theory proposes that the neurotransmitter-tropic filopodial response of astrocytes and/or activity related astrocytic swelling in vitro also occur in vivo where they provide a mechanism that mediates the astrocytic envelopment and segregation of synapses. Just as the extent of filopodial growth in vitro is dependent on neurotransmitter concentration and exposure time and the degree of swelling is dependent on extracellular ionic concentrations, the extent of astrocytic envelopment of synapses in vivo depends on the synapses' firing history. An astrocyte would thus be expected to change its envelopment of individual synapses within the total population of enveloped synapses based on the relative firing frequencies of each synapse. I refer to this in vivo astrocytic movement guided by synaptic activity as *infotropism*.

Astrocytes Control Neurotransmitter Release

Nearly 30 years ago, Katz and Miledi (15) demonstrated that the amount of neurotransmitter released from presynaptic terminals in response to a propagated action potential was related to $[Ca^{2+}]$ in the synaptic cleft. This relationship was hypothesized to be nonlinear, with synaptic release proportional to the fourth power of $[Ca^{2+}]$ (16). Thus, small changes in synaptic cleft $[Ca^{2+}]$ may have relatively large effects on synaptic transmission; indeed, this concept has received recent support (17, 18). Astrocytes that envelop synapses, it is proposed, are able to control synaptic cleft $[Ca^{2+}]$ through mechanisms of the astrocytic calcium wave. Two major events occurring during the astrocytic calcium wave have recently been described (1,2): liberation of intracellular protein bound Ca^{2+} into the astrocytic cytoplasm and simultaneous uptake of Ca^{2+} from the astrocytes' extracellular environment. Indirect evidence also suggests the return of free Ca^{2+} to the extracellular space upon termination of the calcium wave (1). In vivo, astrocytes' ability to rapidly reduce and restore Ca^{2+} in the synaptic clefts they envelop affords them control of neurotransmitter release and, therefore, control of neurotransmission itself (Fig. 1b,c).

Figure 1b

In absence of astrocytic calcium wave, free Ca^{2+} available in synaptic cleft.

Figure 1a

Schematic of one synapse enveloped by filopodial extension of one astrocyte.

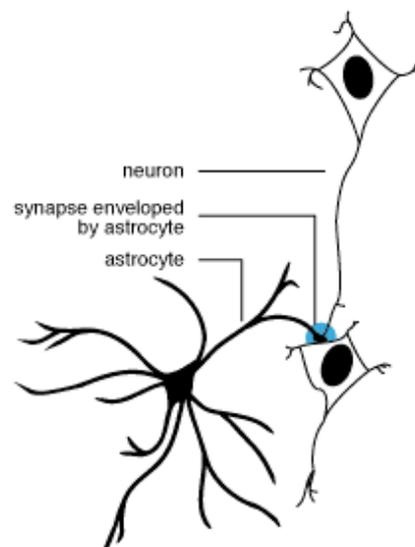
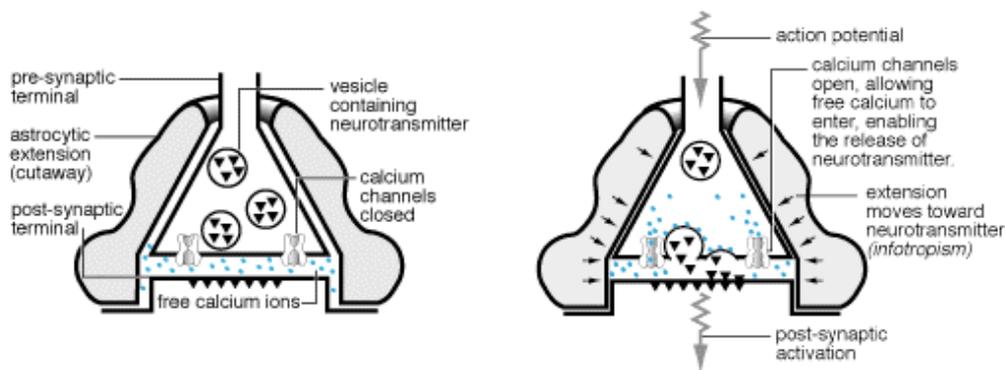


Figure 1c

Free Ca^{2+} allows the release of neurotransmitter resulting in both post synaptic activation and infotropic movement of astrocyte toward neurotransmitter within the synaptic cleft.



Neurotransmitters Evoke Calcium Waves

Astrocytic calcium waves can be evoked *in vitro* by exposure to both excitatory and inhibitory neurotransmitters applied in suprathreshold concentrations (1,2). Although most of the evidence for calcium waves has come from observations *in vitro*, there is some evidence for calcium wave production *in situ* as well (5, 19). This theory proposes that similar astrocytic calcium waves also occur *in vivo*.

It is unlikely that sufficient neurotransmitter would be released at one astrocytically enveloped synapse to provoke a calcium wave in the enveloping astrocyte. One astrocyte, however, can envelop many synapses *in vivo*. Thus, if calcium waves occur *in vivo* within the cortex, coordinated exposure to neurotransmitters at many of the synapses one astrocyte controls could be sufficient to trigger calcium wave production. A reciprocal relationship would then be established between an astrocyte and the synapses it envelops. The astrocyte controls neurotransmitter release through calcium wave modulation of synaptic $[Ca^{2+}]$ and an astrocytic calcium wave is precipitated in turn by coordinated neurotransmitter release at the many synapses that the astrocyte envelops.

These interdependent astrocytic and neuronal events are summarized in Figs. 1b, c above and 2 below. In the absence of either a presynaptic action potential or an astrocytic calcium wave, a high level of Ca^{2+} is available within the extracellular space of the synaptic cleft (Fig. 1b). An action potential arriving at the presynaptic terminal opens the terminal's calcium channels. Extracellular Ca^{2+} enters the terminal and facilitates neurotransmitter release into the synaptic cleft (Fig 1c). The released neurotransmitter activates the postsynaptic terminal. Simultaneously, the astrocyte enveloping the synapse is also exposed to the released neurotransmitter resulting in two consequences: 1) the "infotropic" response of the astrocyte is activated, moving the enveloping astrocyte's surface closer to the highest concentration of neurotransmitter within the synaptic cleft; 2) if the [neurotransmitter] threshold of the astrocyte is exceeded, a calcium wave is generated.

Figure 2a

Astrocytic calcium wave reduces free Ca^{2+} in synaptic cleft.

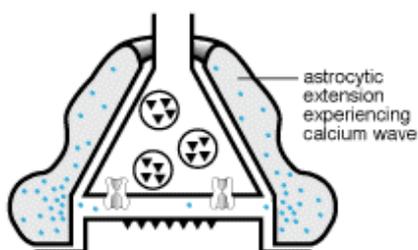
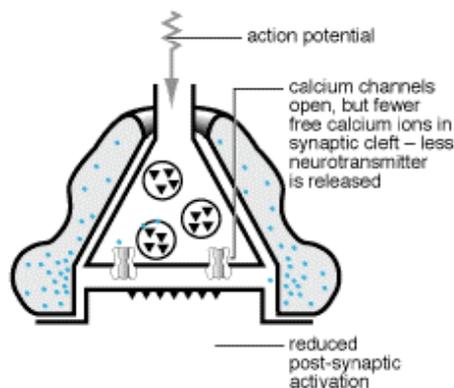


Figure 2b

Despite arriving action potential and open calcium channels, neurotransmitter release is reduced during astrocytic calcium wave.



During a calcium wave, the synaptic environment changes dramatically (Fig 2a). The astrocytic calcium wave reduces Ca^{2+} in the cleft. Decreased $[Ca^{2+}]$ in the cleft inhibits further neurotransmitter release, despite the arrival of action potentials (Fig 2b). Only with cessation of the astrocytic calcium wave will Ca^{2+} return to its original level in the synaptic cleft allowing neurotransmitter release at high levels.

Astrocytes Organize Synapses

By simultaneously regulating neurotransmission in all of the synapses an astrocyte has enveloped, the astrocytic calcium wave may coordinate synapses into synchronously firing groups. Thus, all of the synapses enveloped or partially enveloped by an astrocyte may be within that astrocyte's *domain of synaptic influence*. Fig. 3a illustrates an astrocyte and many of the synapses it envelops. Initiation of a calcium wave in this astrocyte occurs when a sufficient number of presynaptic terminals

Figure 3

Schematic of an astrocyte and its domain of influence (here, eight synapses).

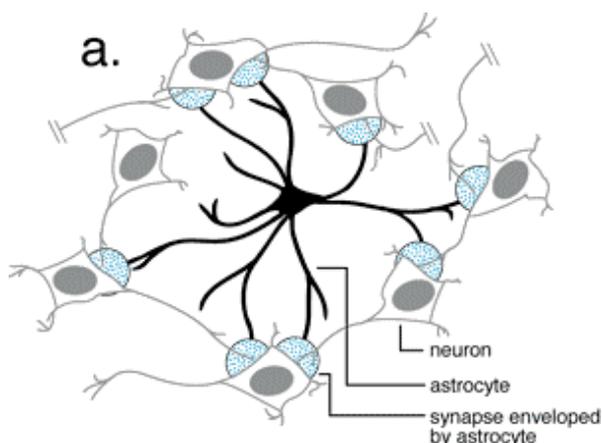
3a. In absence of astrocytic calcium wave, Ca^{2+} available in synaptic clefts.

3b. Neurotransmitter released at four synapses within the domain.

3c. Astrocytic calcium wave results from exposure to neurotransmitter. Ca^{2+} is reduced in synaptic clefts of entire domain inhibiting neurotransmission in all eight synapses.

within its domain of influence release neurotransmitter simultaneously, exposing the astrocyte to suprathreshold stimulation (Fig 3b). During the astrocyte's calcium wave all the synaptic extracellular space within its domain undergoes a decrease in Ca^{2+} , inhibiting neurotransmitter release and neurotransmission throughout the astrocyte's entire domain of influence (Fig. 3c). Termination of the calcium wave shifts Ca^{2+} back into all the synaptic clefts simultaneously. Although calcium channels in each of the synapses within the domain may have opened at different times, the sudden, simultaneous availability of increased Ca^{2+} to all opened channels might be expected to phase lock and synchronize neurotransmitter release. Synchronous neurotransmission throughout the entire domain would be expected as the astrocyte's calcium wave is reinitiated (Fig 3d). Such synchronous neurotransmission, it is hypothesized, might occur at relatively high frequencies in vivo because astrocytes at room temperature in vitro can generate calcium wave oscillations with frequencies of several times per minute (1, 2, 3, 20).

3d. Termination of calcium wave returns previous level of Ca^{2+} to all synaptic clefts resulting in secondary synchronous neurotransmission throughout the domain.



Astrocyte Connections Allow Expanded Control of Synapses

Astrocytes are connected to each other by unidirectional gap junctions that allow the exchange of many biologically important molecules (21, 22). Astrocyte to astrocyte unidirectional transfer of unbound cytoplasmic Ca^{2+} occurs through gap junctions during calcium wave generation (23). The presence of unbound Ca^{2+} within astrocytic cytoplasm is known to facilitate calcium wave activation (23). Inositol 1,4,5-triphosphate (InsP3), which is important in the release of Ca^{2+} from intracellular stores (24), has also been hypothesized to move through gap junctions and play a role in intracellular calcium wave activation and intercellular calcium wave propagation (25). Sequential intercellular propagation of calcium waves may occur as a consequence of the relative combined effects of intercellular Ca^{2+} and/or InsP3 transmission and coincident neurotransmitter stimulation from overlapping domains of synaptic influence. Varieties of calcium wave propagation supporting these contentions have been observed in monolayer and organotypic culture preparations (2, 19, 23). A group of astrocytes acting as a single cell or syncytium may, through the generation of a pervasive calcium wave, control and synchronize the firing patterns of synapses of a great many neurons. This putative coupling of astrocytic and synaptic function implies that the initiation of a calcium wave by a subgroup of synapses within the domain should inhibit neurotransmitter release throughout the entire domain, and this initiation should effect a secondary neurotransmission synchrony in the domain's larger group of synapses. This final array of synchronously firing synapses would be related only in part to the synapses initiating the calcium wave.

At a rate equal to the generation of the astrocyte's calcium wave, the astrocyte would be expected to infotropically increase its influence on the initiating synapses of the subgroup by drawing closer to them, decreasing their extracellular perisynaptic spaces. These decreases in the perisynaptic spaces would not only increase the astrocyte's ability to control extracellular Ca^{2+} but would also, by increasing concentration of released neurotransmitter within a now more restricted synaptic cleft, increase the synapses' efficiency in provoking a calcium wave. Such an activity-dependent change in the astrocytic calcium wave response, apparently being potentiated by previous episodes of activity in nearby synapses, has recently been demonstrated in situ (5). This reciprocating relationship might enable an even smaller subgroup of presynaptic terminals within the astrocyte's domain to precipitate a calcium wave, in turn affecting neurotransmission within the entire domain of synapses.

After the pervasive and synchronous neurotransmitter release throughout the astrocyte's domain of influence, a calcium wave is again initiated. A reciprocating relationship between calcium wave activation and synchronous neurotransmitter release would be expected to continue as long as enough presynaptic terminals are releasing sufficient quanta of neurotransmitter to exceed the astrocyte's calcium wave threshold. The frequencies of these astrocytic-synaptic oscillations would be dependent upon and reflective of both the character and duration of the initiating stimuli.

From this vantage, this theory proposes that sensory information is encrypted by associative cortex in patterns of synchronous synaptic firing that are determined by varying patterns of astrocytic syncytia. Astrocytic-synaptic oscillations occur at various frequencies for various periods of time. The spatial patterns, frequencies and duration of these oscillations are dependent on both the sensory input creating them and the influences of pre-established astrocytic domains of influence.

The Input Changes the Hardware

It has traditionally been held that associative cortical integration of sensory input is accomplished purely through utilization of complex networks of neuronal connections. The theory presented here, however, contends that the associative areas of brain include plastic, motile astrocytes that participate in the encoding and manipulation of information by organizing and controlling groups of synapses. Sensory information that began its journey as neuronal action potentials eventually reaches areas of the central nervous system in patterns that activate astrocytic calcium waves. According to the theory, activated astrocytes in turn infotropically encode the information with resulting synchronously firing synaptic domains. The character of the synaptic domains reflects the primary perceived sensory information at any moment in time, but the pools of synchronous synapses are modified by the presentation of novel information. Through the mechanism of infotropic astrocytic movement, metaphorically speaking, 'the input changes the hardware.'

The theory predicts that repetitive, identical activation patterns of sensory cortices will be mirrored in repetitive infotropic responses of associative cortical astrocytes and the creation of representational domains of influence. Because each synapse and astrocyte may participate in a host of infotropically encoded patterns which reflect the character, duration and chronology of sensory input, individual synaptic or astrocytic activations have deterministic meaning only in the context of their place in activation sequences.

Applying the Theory of Neuron-Astrocyte Interaction

The theory of neuron - astrocyte interaction may be useful in provoking a reformulation of concepts of some disorders affecting the nervous system. The following sections consider epilepsy, minor head trauma, and the effects of neuron-astrocyte interaction on gap junction blockage and associative memory.

Is Epilepsy an Astrocytic Disorder?

No universally accepted hypothesis has yet been offered that explains the varieties of rhythmic and synchronous neuronal firing that define epileptic seizures. Many investigators have suggested, however, that astroglia play a significant role in epilepsy (26, 27, 28). This theory allows for synchronous neuronal firing involving the domains of many astrocytes acting as a syncytium. A calcium wave produced by millions of astrocytes acting as a syncytium would, at the wave's termination, be expected to result in the synchronous firing of neurons in large regions of the brain. The widespread, coordinated release of neurotransmitter would then precipitate a second equally pervasive calcium wave in the astrocytic syncytium, which again would effect synchronous neuronal firing, and so on, resulting in the synchronous and rhythmic neuronal firing characteristic of the epileptic seizure. Epilepsy, this theory contends, is primarily a disorder of astrocytes caused by pathological, high frequency syncytial calcium waves preceding and modulating a consequential neuronal synchrony. Varieties of seizures, according to this theory, are dependent on the extent and character of the pathologically large astrocytic syncytia producing them.

The partial complex seizures of childhood known as *petit mal* may provide an example of the astrocytic etiology of epilepsy. *Petit mal* seizures can often be provoked by hyperventilation (for example, by having a child blow repeatedly on a pinwheel). After several minutes of hyperventilating the pH of the child's blood becomes slightly alkaline as a consequence of the respiratory depletion of carbon dioxide. With this shift toward the alkaline, the *petit mal* seizure begins as evidenced by a characteristic three-per-second spike-wave pattern on the electroencephalogram. In addition to their many other roles, astrocytes near the capillaries of cerebral cortex envelop these blood vessels with their cytoplasmic extensions. The exposure of these perivascular astrocytes, which also control synaptic domains of influence, to the sudden alkaline shift in the blood may result in primary perivascular calcium wave activation and secondary perivascular synaptic synchrony. Indeed, the three-per-second spike-wave pattern seen on the electroencephalogram may reflect the synaptic (spike) and astrocytic (wave) oscillations the theory proposes, with unusually high frequency calcium waves resulting from the effects of alkalosis combined with secondarily coordinated neurotransmitter release. Of additional interest is the demonstration that many of the medications used in the treatment of epilepsy are astrocytic calcium wave inhibitors (29, 30).

Does Minor Head Trauma Create Nonsense Calcium Waves?

Equally mysterious are the mechanisms producing unconsciousness resulting from minor head trauma insufficient in force to cause any detectable injury. Mechanical perturbation has been shown to precipitate calcium waves in vitro (20). A blow to the head results in a mechanical compression wave traveling through the brain. This mechanical force could be sufficient to produce a pattern of widespread sequential calcium waves that reflect the shape and velocity of the mechanical compression wave. The astrocytic calcium waves so produced would be unrelated to, and for a while unresponsive to the influence of, normal sensory input. Meaningful interactions between astrocytes and synapses could be overwhelmed by the disruptively nonsensical mechanically induced calcium wave patterns. Despite the inability of the mechanical force to produce macro or microscopic injury, the brain -- the person -- would be "knocked out" or temporarily unconscious.

Do General Anesthetics Work by Blocking Astrocytic Gap Junctions?

A similar unconscious state in which the cellular elements of associative cortex cannot respond normally to sensory input could, according to the theory, result from astrocytic gap junction blockade. Without functional gap junctions, astrocytes become unable to transmit their control of synchronous synaptic firing through the cortex. Because astrocytes cannot form syncytia, their control is restricted to only the synapses within their individual domains of influence. Several general anesthetics have been demonstrated to be reversible gap junction blockers (21, 31).

Does Memory Depend on the Neuron-Astrocyte Relationship?

Many authors have speculated on the involvement of astrocytes in memory and CNS plasticity (32, 33). The neuron-astrocyte theory here, however, proposes that the infotropic character of astrocytes is crucial to the cellular basis of associative memory. Also, *neuroplasticity* may more properly be termed *neuronal-astrocytic plasticity*, with the astrocytes' capacity to influence groups of synapses compromised only by the degree to which they have already organized these groups. Biological imprinting that occurs within defined critical periods of many species might represent a more permanent infotropically mediated astrocytic organization of synaptic domains. This premise is supported by the work of Muller and Best (34), who reinduced ocular-dominance plasticity in adult animals by supplementing the adult visual cortex with astrocytes cultured from the visual cortex of newborn animals.

Concluding Remarks

The neuron-astrocyte theory challenges the notion that neuronal networks alone, no matter how complex, can explain the many normal and pathological aspects of brain function. This model, in which motile astrocytes organize and modulate synaptic activity, may permit widely divergent aspects of brain function and pathology to be viewed from a single theoretical vantage. Testing key aspects of this theory, i.e., astrocytic movement in vivo and astrocytic control of neurotransmission in vivo, will present significant technical challenges. When these challenges are overcome, however, we may learn significant new lessons about cortical function, its cellular substrates, and the mechanisms by which it is compromised in a variety of disease states.

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and K. Fretwell for providing the illustrations.

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Re: A Theory of Cortical Neuron-Astrocyte Interaction (Score 1)
 by: mhalassa on: Saturday 28 July @ 02:43:21
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A recent report shows that astrocytes generate calcium oscillations spontaneously in acutely isolated brain sections (*Nature Neuroscience* 2001; 4(8):803-12). This finding might have additional insight into the physiological significance of glial modulation of neuronal excitation in vivo, as now glia have been shown to release their glutamate without activity originating from neurons. This poses a question on the whole neuron-glia feedback loop that has been suggested earlier by many scientists.

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Re: A Theory of Cortical Neuron-Astrocyte Interaction (Score 0)
 by: Anonymous on: Thursday 21 June @ 18:07:31

As much as this theory sounds exciting and credible, it seems to lack much of the in vivo evidence that one would look for.

I don't know of any single experiment that suggests astrocytic calcium waves happen in the intact brain.

This problem, moreover, has never been tackled by Genetics, which is the only way to prove the in vivo relevance for all the tissue culture work that has already been worked out.

Another issue I would like to comment on, is the fact that the aforementioned theory discusses brain astrocytes as a homogenous cellular population. Many reports have emerged lately to suggest otherwise,

for example, GFAP, which some consider the universal astrocytic marker is variably expressed by astrocytes in various brain regions.
I am still a big fan of the theory though!!
Reply to:ferroportin@hotmail.com

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Re: A Theory of Cortical Neuron-Astrocyte Interaction (Score 1)
by: mhalassa on: Saturday 23 June @ 04:24:22
([User Info](#))

One interesting phenomenon that has been ignored throughout this whole story, is the fact that astrocytes can release neurotransmitters and neuromodulators through mechanisms that are yet to be discovered (Wolosker et al, PNAS 1999, 96:13409-14). The author, moreover, mentions a somewhat negative-feedback relationship between neuronal firing and astrocytic calcium waves. It has been recently shown, however, that astrocytic calcium waves can cause glutamate mediated currents to happen in adjacent neurons (Parpura et al, PNAS 2000, 97:8629-34). I think that the theory should be updated regularly to include recent research data. Maybe an update team would do!

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