



Centre for
Pain Medicine

STERILE INFLAMMATION

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STERILE INFLAMMATION groups

- **Autoimmune diseases**
- **Systemic inflammatory conditions**
 - Osteochondrosis
 - Arteriosclerosis
- **Catastrophic events**
 - Trauma (inclusive surgery)
 - Vascular occlusion
- **Unresolved immune actions**
 - Cancer (some forms)
 - Glomerulonephritis
 - Endometriosis
 - Posttraumatic residual inflammation
 - Spinal pain – tendinitis – other nociceptive and neuropathic pain



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unresolved immune actions (2)

- **Neuroinflammatory diseases**
 - Parkinson
 - Amyotrophic Lateral Sclerosis
 - Alzheimer disease
 - Cerebellar degeneration
- **Inflammatory psychiatric disorders**
 - Major Depressive Disorder (MDD)
 - Schizophrenia
 - Bipolar disorder
 - Autism
 - ADHD
 - Posttraumatic stress disorder
 - Emotional stress
- **Ophthalmological diseases**
 - Age related Macular Degeneration (AMD)

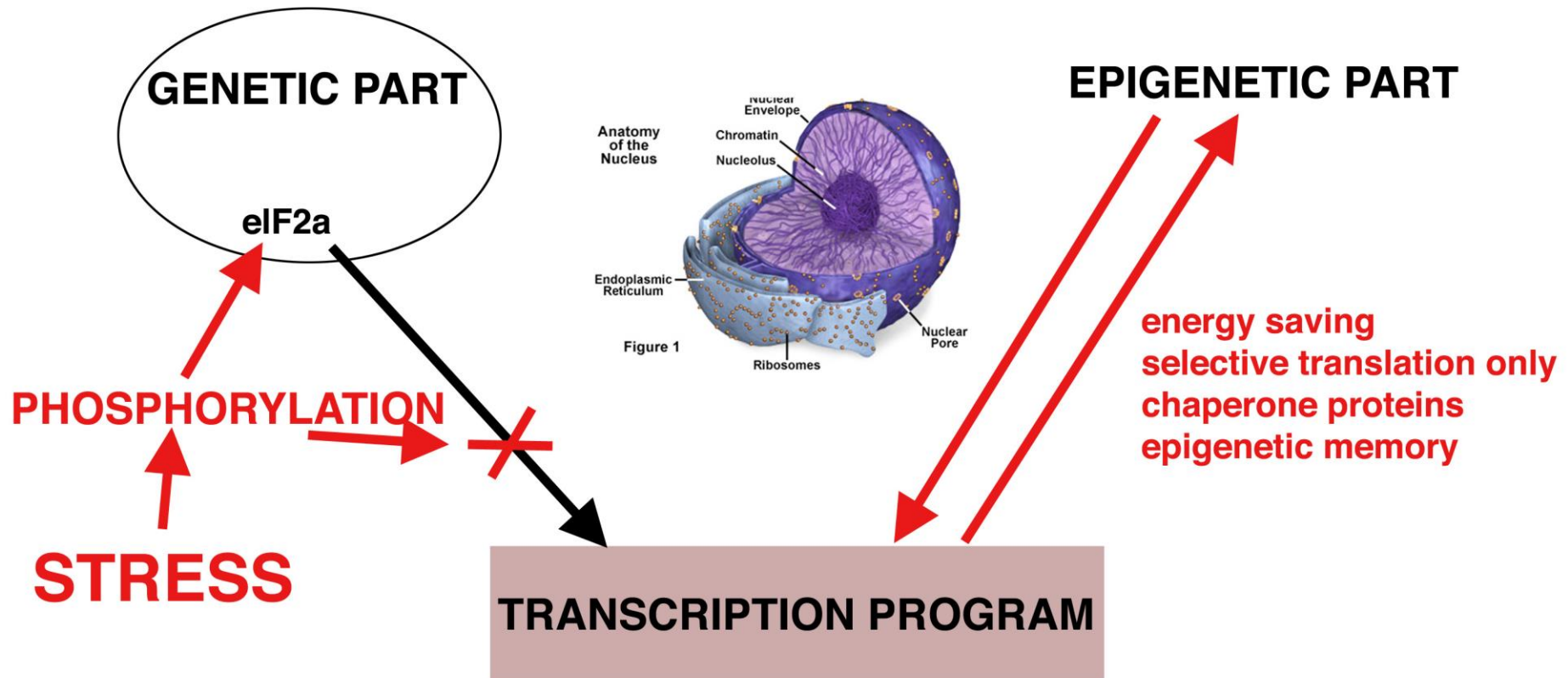


STERILE INFLAMMATION pathology

- **Cellular level**
 - The transfer of control
 - Oxidative stress
 - The redox equilibrium
 - Epigenetic marks
- **From the periphery to the brain**
 - Nervous pathway
 - Intravascular cytokines
- **From the brain to the innate immune system**
 - The sympathetic nervous system
 - The HPA axis
- **The everlasting battle: the unresolved immune action**



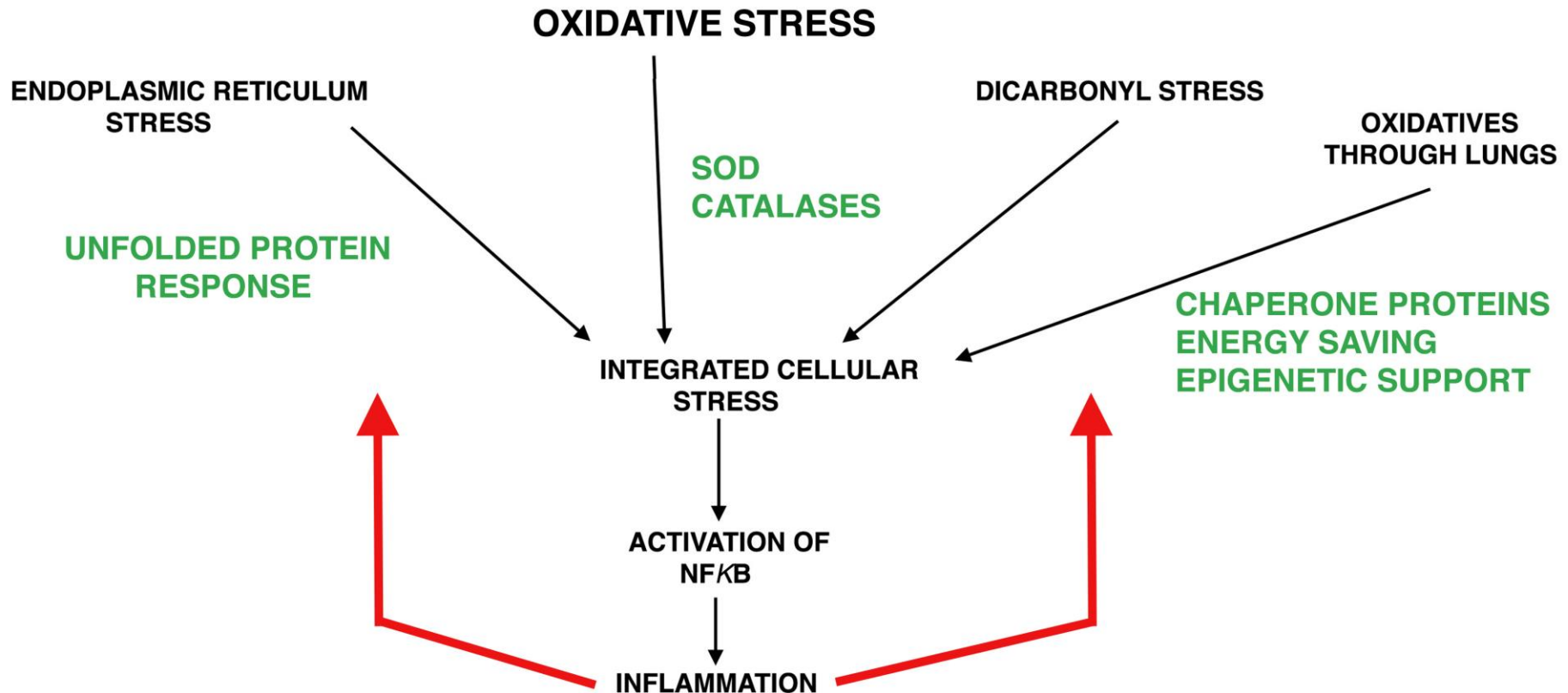
STERILE INFLAMMATION the initiation of cell stress





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cellular stress





CELL STRESS

the epigenetic part of chromatin

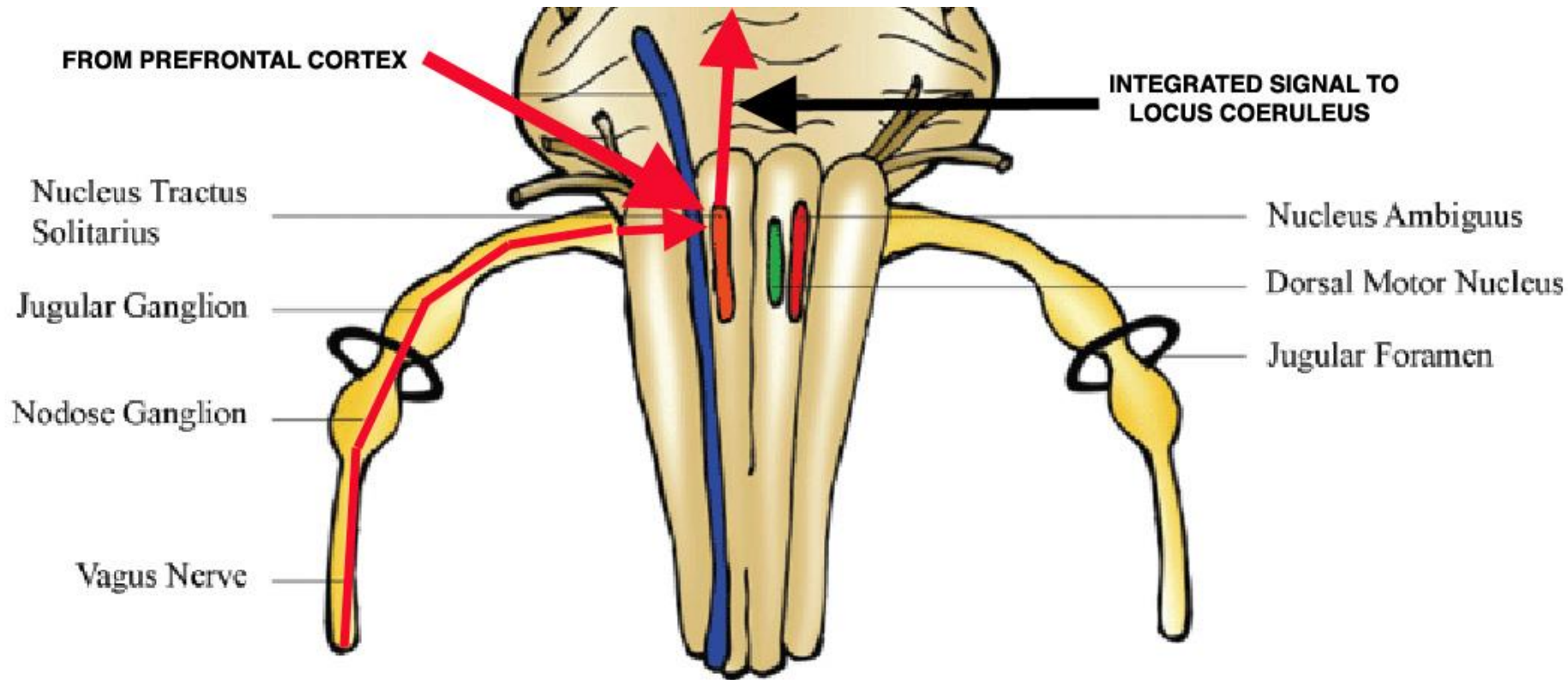
- **May protect the cell because it knows how to deal with a specific form of stress**
- **Is known to persevere – sometimes – in a response even if the factors causing the response have changed**
- **Epigenetic changes:**
 - Methylation/demethylation
 - Posttranslational histone modifications
 - (uncoded) microRNAs



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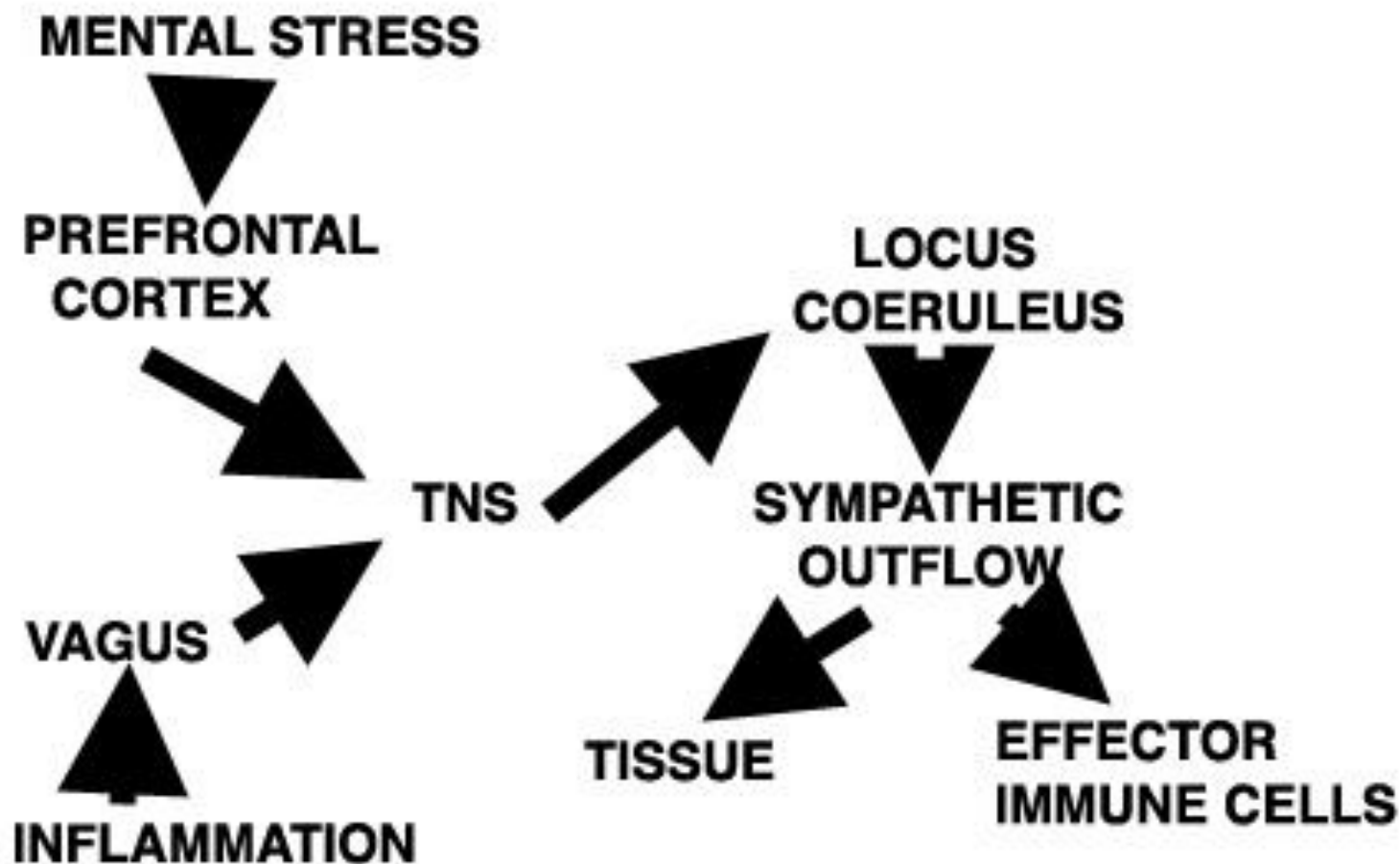
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integration of somatic and mental stress in NTS





From stress to immune response





OXIDATIVE STRESS

1990-2000: The period of lament

- **Oxidative stress tends to initiating a negative cycle**
 - Each destructive action consumes an electron
- **chain reactions are common**
- **Experience with anti-oxidant substances has been disappointing**
 - The “anti-oxidant paradox”
- **Oxidative stress may therefore cause significant secondary tissue damage**
 - **Following vascular occlusion**
 - Coronary infarction
 - Stroke
 - Intentional vascular occlusion
 - **Following trauma**
 - **Following prolonged inflammation**



OXIDATIVE STRESS

■ Counterarguments

- Transfer of electrons is the basis of aerobic life
- Transfer of electrons implies the presence of radicals
- Radicals play a crucial role in intracellular signaling
 - Cross talk with Ca^{2+} ions
 - Second messengers
- Additionally, nature could not foresee old age



Albert Szent-Gyorgyi



- **Based on work by Nordenstrom (1993)**
 - Cancer metastases
 - Low intensity DC
 - Using the vascular tree as a postman for E-fields
- **Self experiments**
 - Iv PRF is uneventful procedure
 - Causes a fall in CRP
 - Causes (?) mood and energy improvement
- **No realistic prospects //**



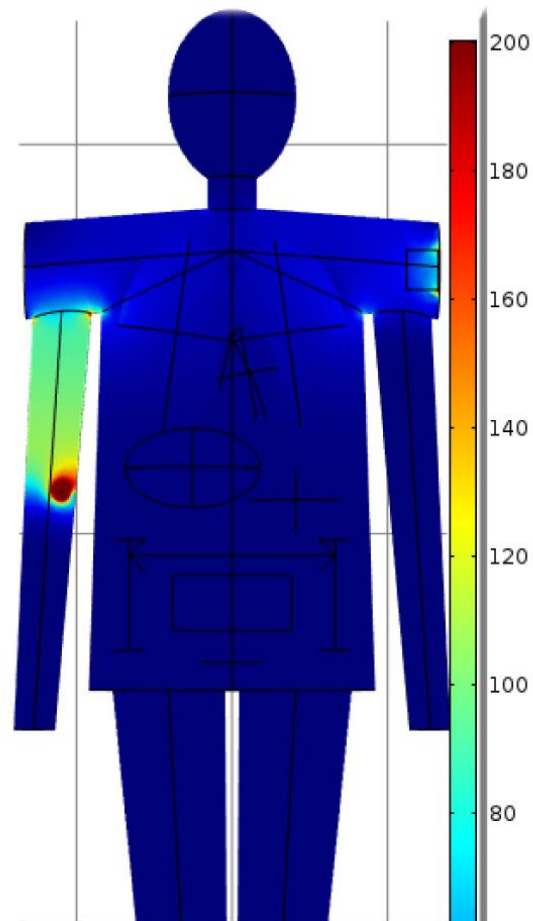
- **PRF**
 - **Eliciting Electric fields in the physiological range**
 - **With a reduced duty load**
 - **Large currents**
 - **Non-invasive**
 - **Choice between general and regional application**
 - **Effective against oxidative stress**
 - **Without any effect on healthy cells**



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Finite element computer simulation of IV PRF

S.Rampersad, Radboud Medical Center; 2014



0-200 V/m

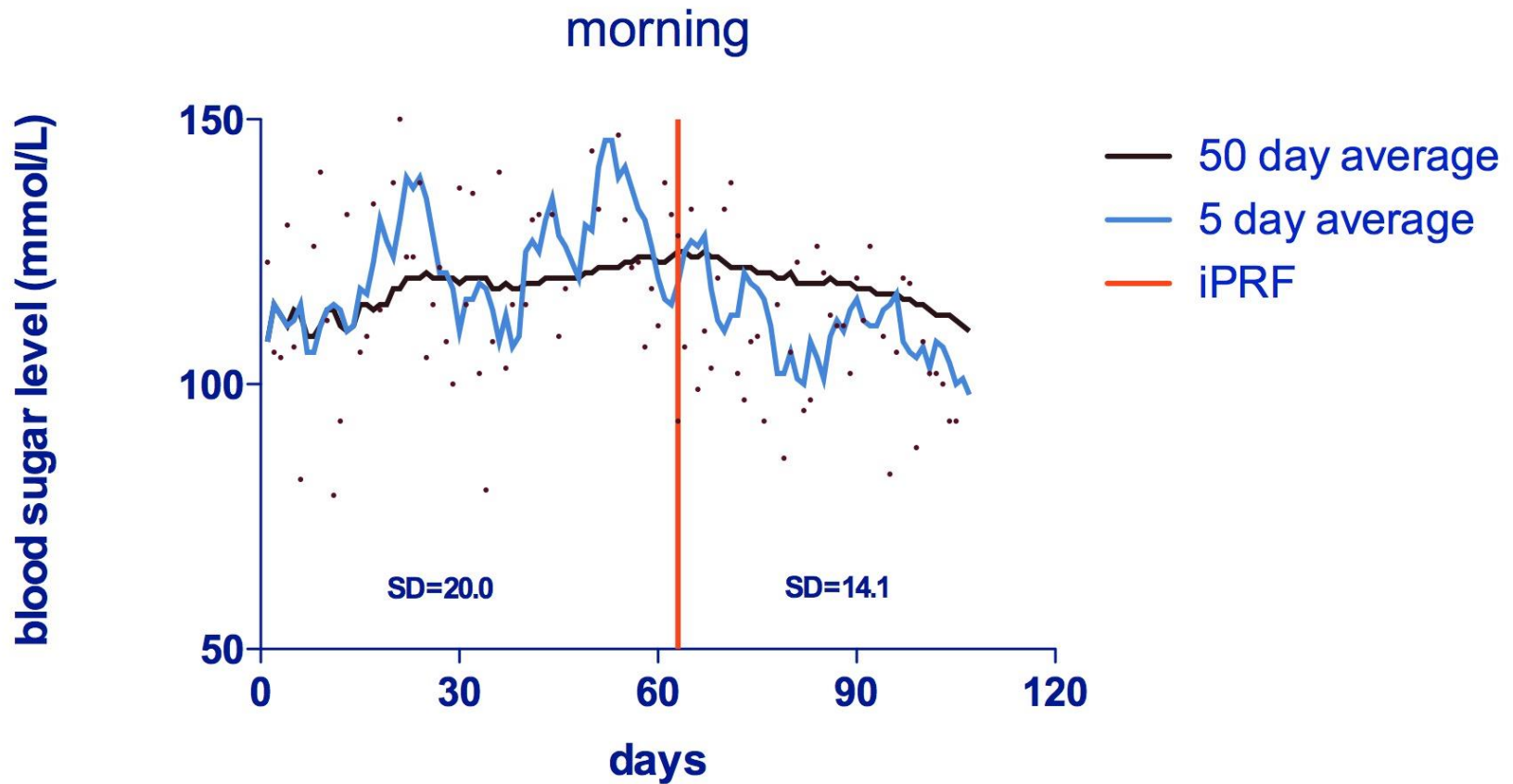


Responses to redoxPRF observations

- **A. A quasi-immediate inflammatory response if antigens or non-self material are present**
 - Healing of infected wounds
- **B. An attractor switch of the ANS to vagus control**
 - Latent period of 12 – 72 hrs
 - Duration up to 2 weeks
- **C. A strong anti-inflammatory effect**
 - Long duration (1 – 6 months)
 - Persisting trend
- **D. Long term: (probably) Epigenetic changes**

redoxPRF

effect on diabetes type 2





redoxPRF

hypothesis on the mode of action

- **A quasi-instantaneous effect on the redox equilibrium of stressed cells**
 - Physical effect?
 - Enzymatic effect?
- **Secondary effects**
 - Reduction of oxidative stress
 - Reduction of sympathetic outflow
 - Correction of the reactivity of effector immune cells
 - ANS attractor change to vagal control
- **Epigenetic change**
 - Memory of the optimal response
 - Prolonging the effect of treatment



redoxPRF is NOT stimulation

- **Stimulation**
 - Elicits a cell response
 - Has no memory
- **redoxPRF**
 - Does not elicit a cell response
 - Basic frequency of RF >> physiological limit
 - Effect is memorized as an epigenetic mark



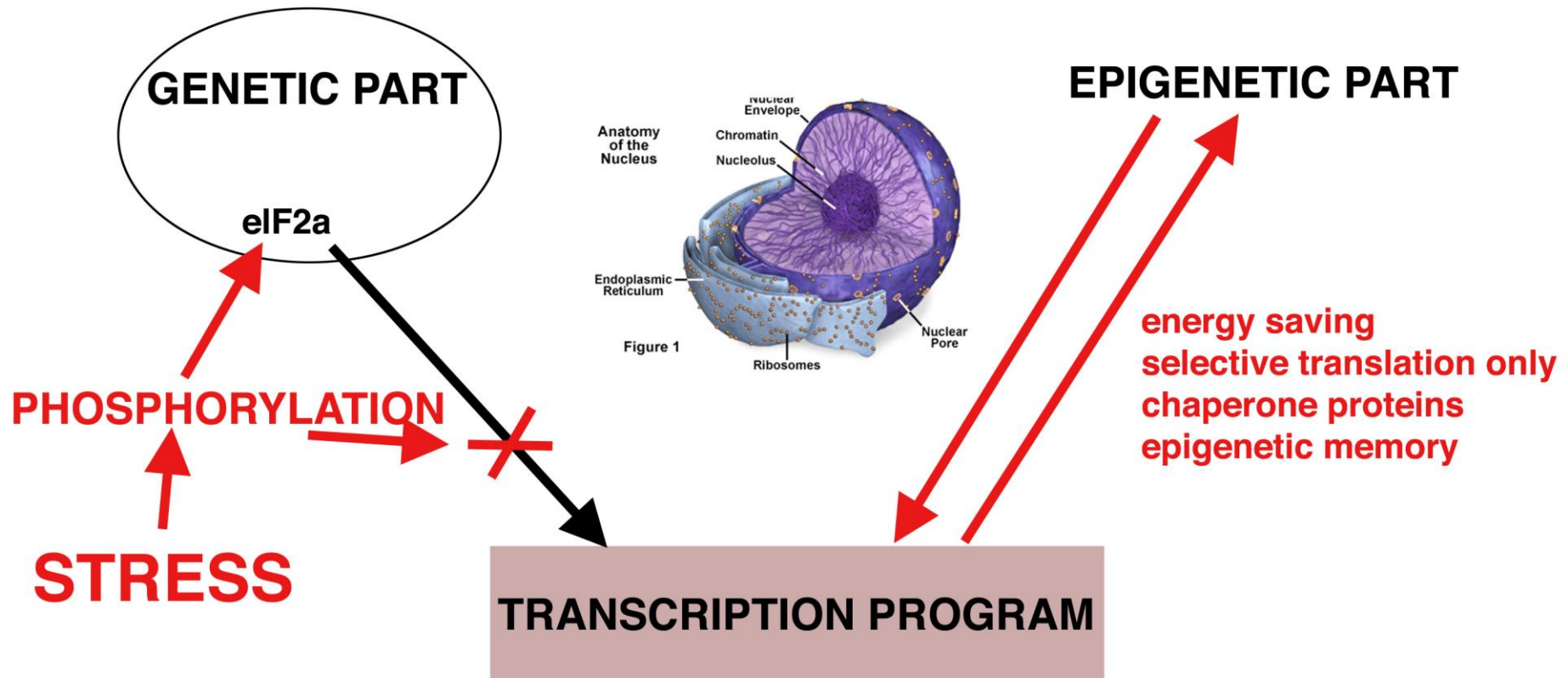
- **Technical issues**
 - General vs local
 - Interval between treatments should be commensurate to pathology
- **Plasticity of the target structure**
 - Lung: good prospects, long intervals will probably suffice
 - Neuroinflammatory diseases: no plasticity. Lost neurons are not replaced
- **Pathology of the cause of cell stress**
- **Availability**
 - redoxPRF is not (yet) a take home device such as TENS



- **Acute inflammatory situations**
 - Vascular occlusion
 - Multitrauma?
- **Chronic inflammation**
 - If target has plasticity
 - Inflammaging?
- **Post infection syndromes**
 - Lyme disease
 - Mononucleosis
 - Psychiatric inflammatory conditions?



STERILE INFLAMMATION the initiation of cell stress





Dot plot showing IL-6 levels (pg/ml) for three groups: controls, asymptomatic SCI, and SCI + pain. The y-axis is logarithmic with values 0, 2.7, 7.4, 20.1, and 54.6. Controls and asymptomatic SCI groups show low IL-6 levels (mostly below 3 pg/ml). The SCI + pain group shows significantly higher IL-6 levels, with a mean around 18 pg/ml and an asterisk indicating statistical significance.

Clinical Correlates of Elevated Serum Concentrations of Cytokines and Autoantibodies in Patients With Spinal Cord Injury

Arch Phys Med Rehabil 2007;88:1384-93.