Chronic Fatigue Syndrome

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Holmes et al criteria (1988)

Major criteria

1. new onset of persistent or relapsing, debilitating fatigue in a person without a previous history of such symptoms that does not resolve with bedrest and that is severe enough to reduce or impair average daily activity to less than 50% of the patient's premorbid activity level for at least 6 months;
2. fatigue that is not explained by the presence of other evident medical or psychiatric illness

Minor Symptom Criteria

1. Mild fever (37.5°-38.6°C orally) or chills
2. Sore throat
3. Posterior cervical, anterior cervical, or axillary lymph node pain
4. Unexplained generalized muscle weakness
5. Muscle discomfort or myalgia
6. Prolonged (at least 24 h) generalized fatigue following previously tolerable levels of exercise
7. New, generalized headaches
8. Migratory noninflammatory arthralgias
9. Neuropsychiatric symptoms, photophobia, transient visual scotoma, forgetfulness, excessive irritability, confusion, difficulty thinking, inability to concentrate, depression
10. Sleep disturbances (hypersomnia or insomnia)
11. Patient's description of initial onset of symptoms as acute or subacute

Physical Examination Criteria

Must be documented by a physician on at least two occasions, at least 1 month apart:

1. Low-grade fever (37.6°-38.6°C orally or 37.8-38.8°C rectally).
2. Nonexudative pharyngitis.
3. Palpable or tender anterior cervical, posterior cervical, or axillary lymph nodes (< 2 cm in diameter).

Fukuda et al (1994)

1. CFS is clinically evaluated, unexplained, persistent or relapsing chronic fatigue that is of new or definite onset (i.e. not lifelong); the fatigue is not the result of ongoing exertion, is not substantially alleviated by rest, and results in substantial reductions in previous levels of occupational, educational, social, or personal activities.

2. There must be concurrent occurrence of four or more of the following symptoms, and all must be persistent or recurrent during 6 or more months of the illness and not predate the fatigue:
    1. Self-reported persistent or recurrent impairment in short-term memory or concentration severe enough to cause substantial reductions in previous levels of occupational, educational, social, or personal activities
    2. Sore throat
    3. Tender cervical or axillary lymph nodes
    4. Muscle pain
    5. Multiple joint pain without joint swelling or redness
    6. Headaches of a new type, pattern or severity
    7. Unrefreshing sleep
    8. Postexertional malaise lasting more than 24 hours

Canadian Criteria (1)

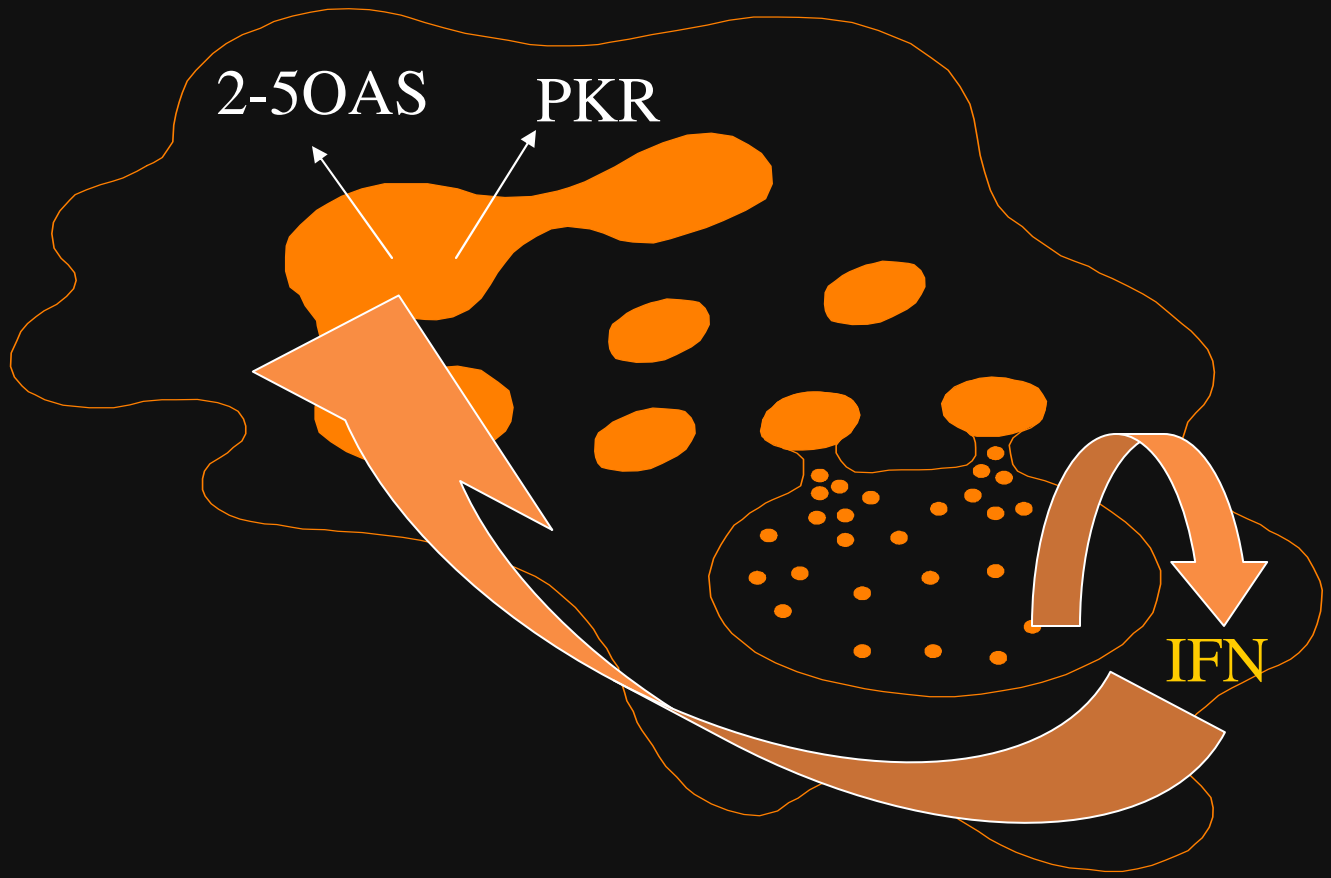
- Fatigue
- Post-exertional malaise and/or fatigue
- Sleep dysfunction
- Pain
- Two or more neurological/cognitive manifestations:
  - Confusion
  - Impairment of concentration and short term memory consolidation
  - Disorientation
  - Difficulty with information processing, categorizing and word retrieval
  - Perceptual and sensory disturbances
  - Ataxia
  - Muscle weakness
  - Fasciculations

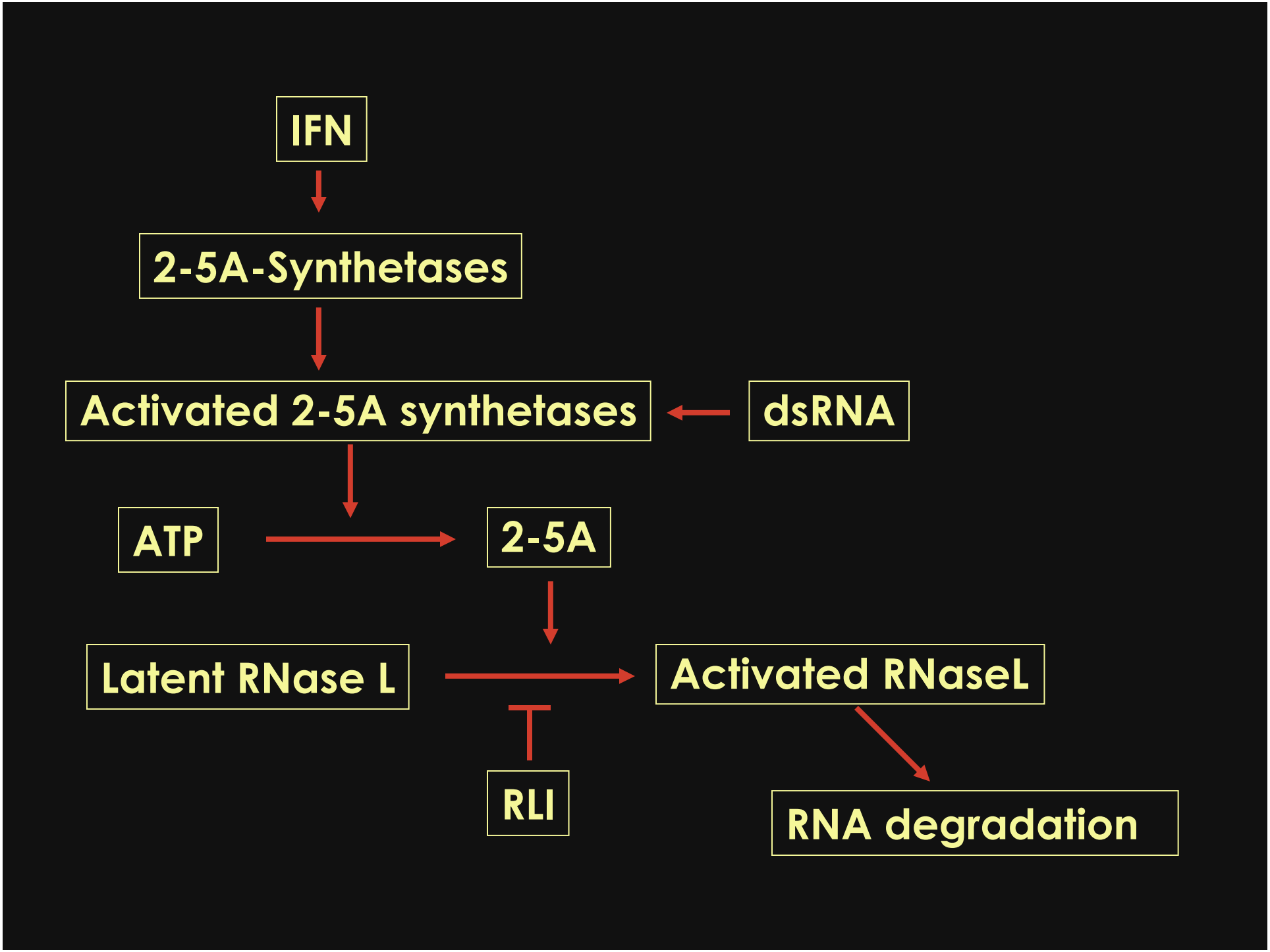
Canadian Criteria (2)

- One or more autononomic/neuroendocrine/immune symptoms:
  - Orthostatic intolerance/neurally mediated hypotension
  - Postural orthostatic tachycardia syndrome
  - Delayed postural hypotension
  - Light-headedness
  - Extreme pallor
  - Nausea
  - Irritable bowel syndrome
  - Urinary frequency and bladder dysfunction
  - Palpitations with or without cardiac arrhythmias
  - Exertional dyspnea

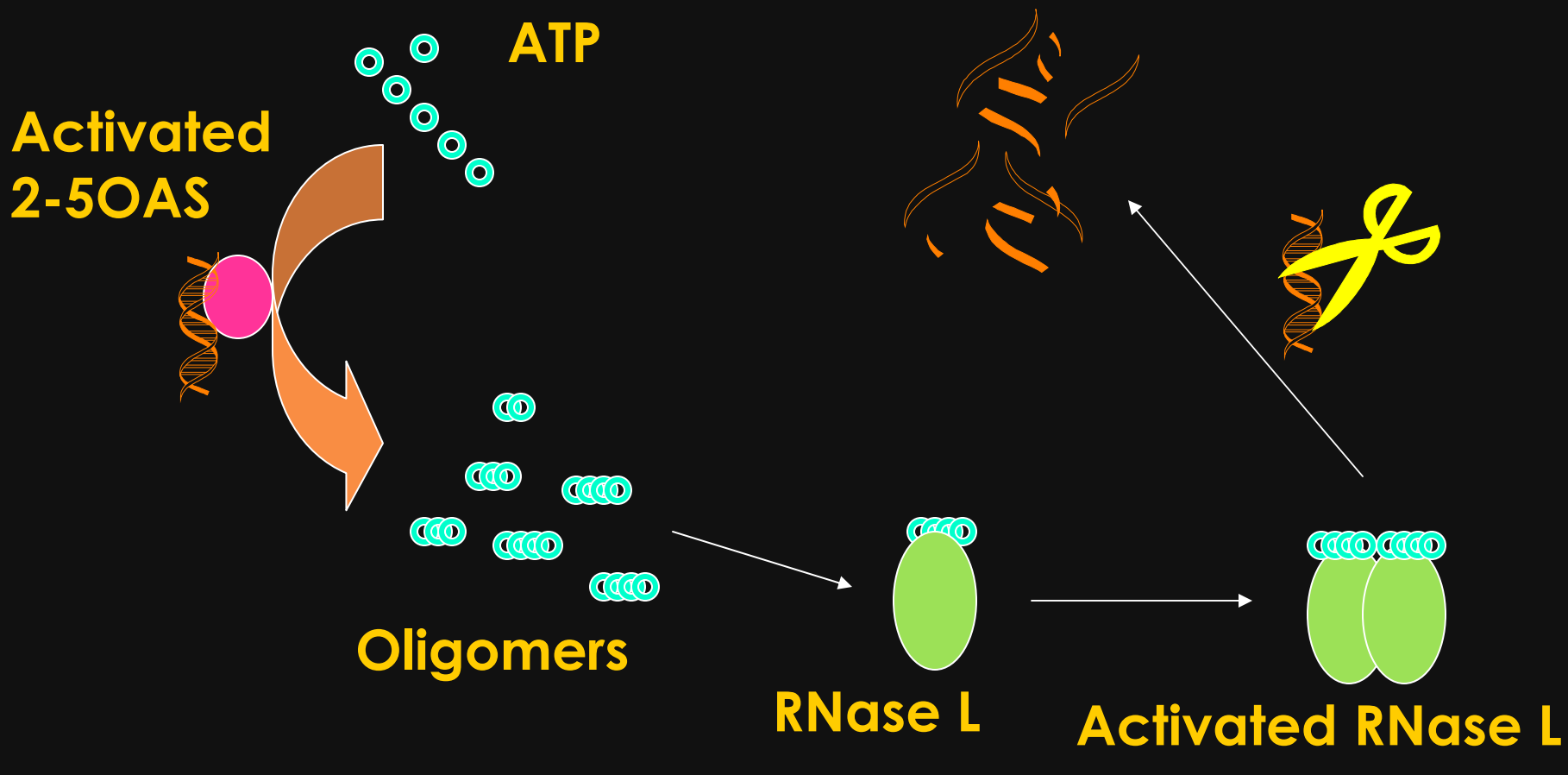
- Illness persists for at least six months, usually distinct onset (may be gradual), for children: three months

Infectious agents invading a cell release RNA or DNA during replication, which induces the production of interferons (IFN) which trigger the development of a defensive response led by two enzymes called 2-5OAS and PKR

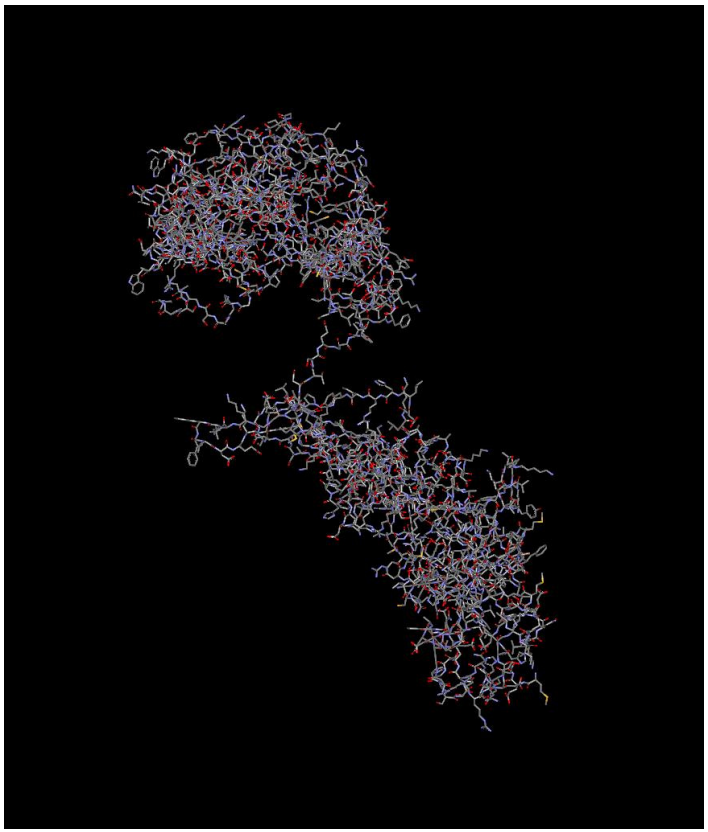



IFN
2-5A-Synthetases
Activated 2-5A synthetases
dsRNA
ATP
2-5A
Latent RNase L
Activated RNaseL
RLI
RNA degradation

2-5OAS is activated by infectious RNA to polymerize ATP into oligomers made of 2 to 5 building blocks. These bind to and activate a latent ribonuclease (RNase L) which destroys infectious and cellular RNA. Infectious agent cannot replicate and the cell dies by suicide (apoptosis) which impairs spreading of the infection.

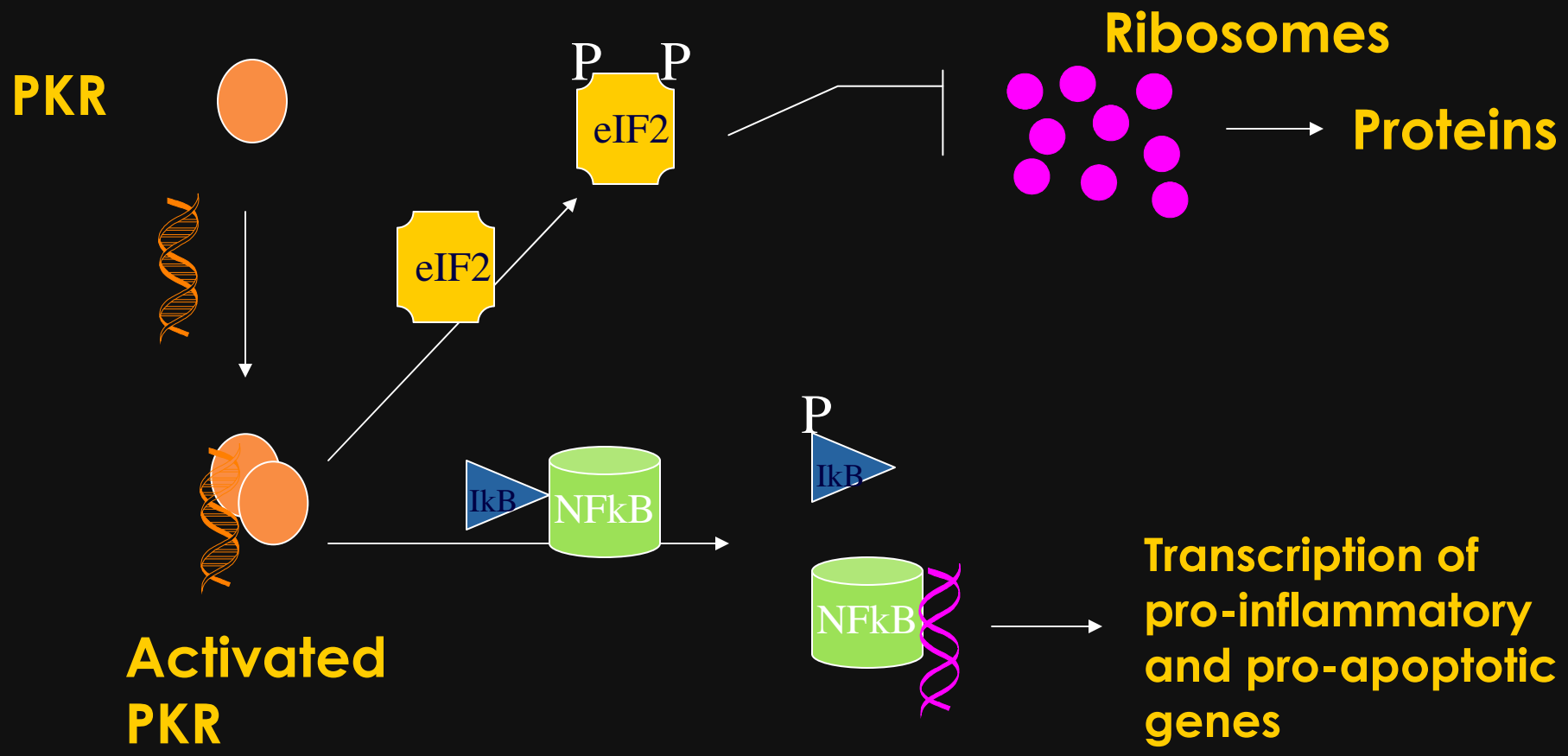


Ribonuclease L is a latent enzyme which, when activated, cleaves infectious and cellular RNA



This activity impairs the replication of the infectious agent and leads to cell suicide (apoptosis)

PKR is activated by infectious RNA to phosphorylate eukaryotic translation initiation factor (eIF2) and the inhibitor (IkB) of the nuclear factor kB (NFkB). The desactivation of these factors leads to the blockade of translation (protein synthesis) by eIF2 and transcription of pro-inflammatory and pro-apoptotic genes by NFkB. The infected cell dies by suicide.

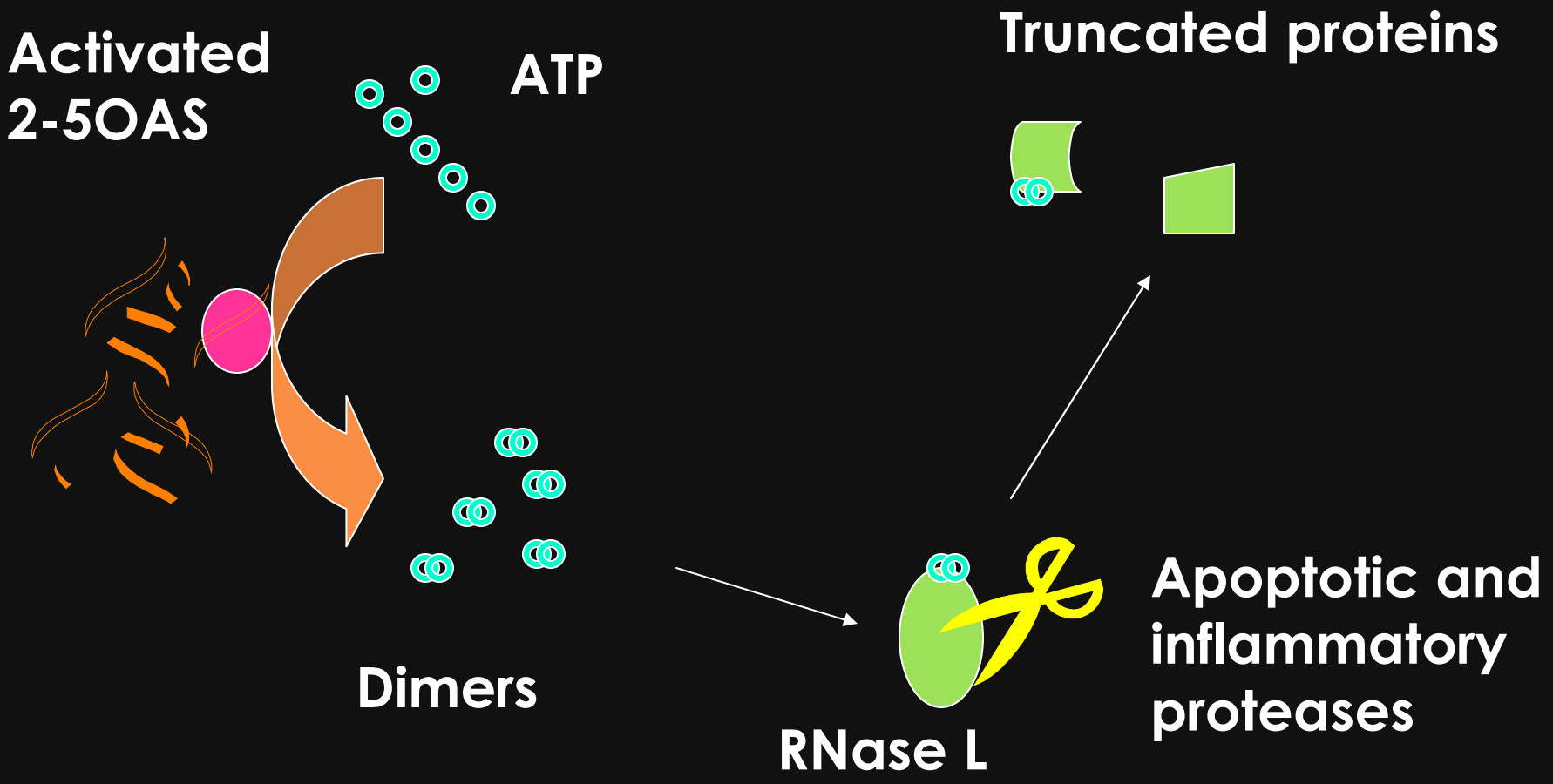


In some stress situations, the cell produces odd RNA/DNA sequences resulting from:

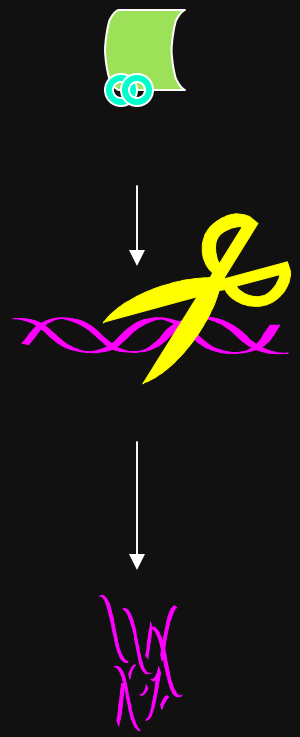
- The expression of endogenous retroviruses sequences (viruses that have retrotranscribed their RNA sequences into our genome during evolution without any control from our gene machinery).
- Release of DNA/RNA fragments from cell damage due to ionizing radiations
- Release of chemically modified RNA/DNA fragments due to toxic chemicals, heavy metals...

These abnormal nucleotides activate the innate cellular immunity mechanisms.
However, this fine-tuned machine does not work as expected.
This process leads to various cellular and immune dysfunctions.

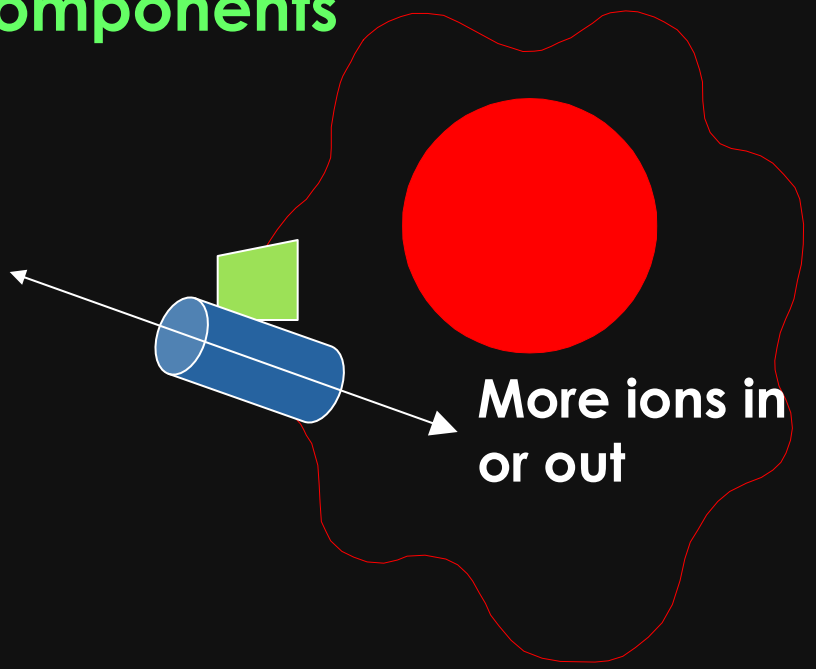
2-5OAS is activated to polymerize ATP into oligomers made of 2 building blocks only. These bind to but fail to activate RNase L by homodimerization. The ribonuclease is cleaved by apoptotic and inflammatory proteases and truncated forms of the protein are generated.



The truncated RNase L fragments act as unregulated cellular components

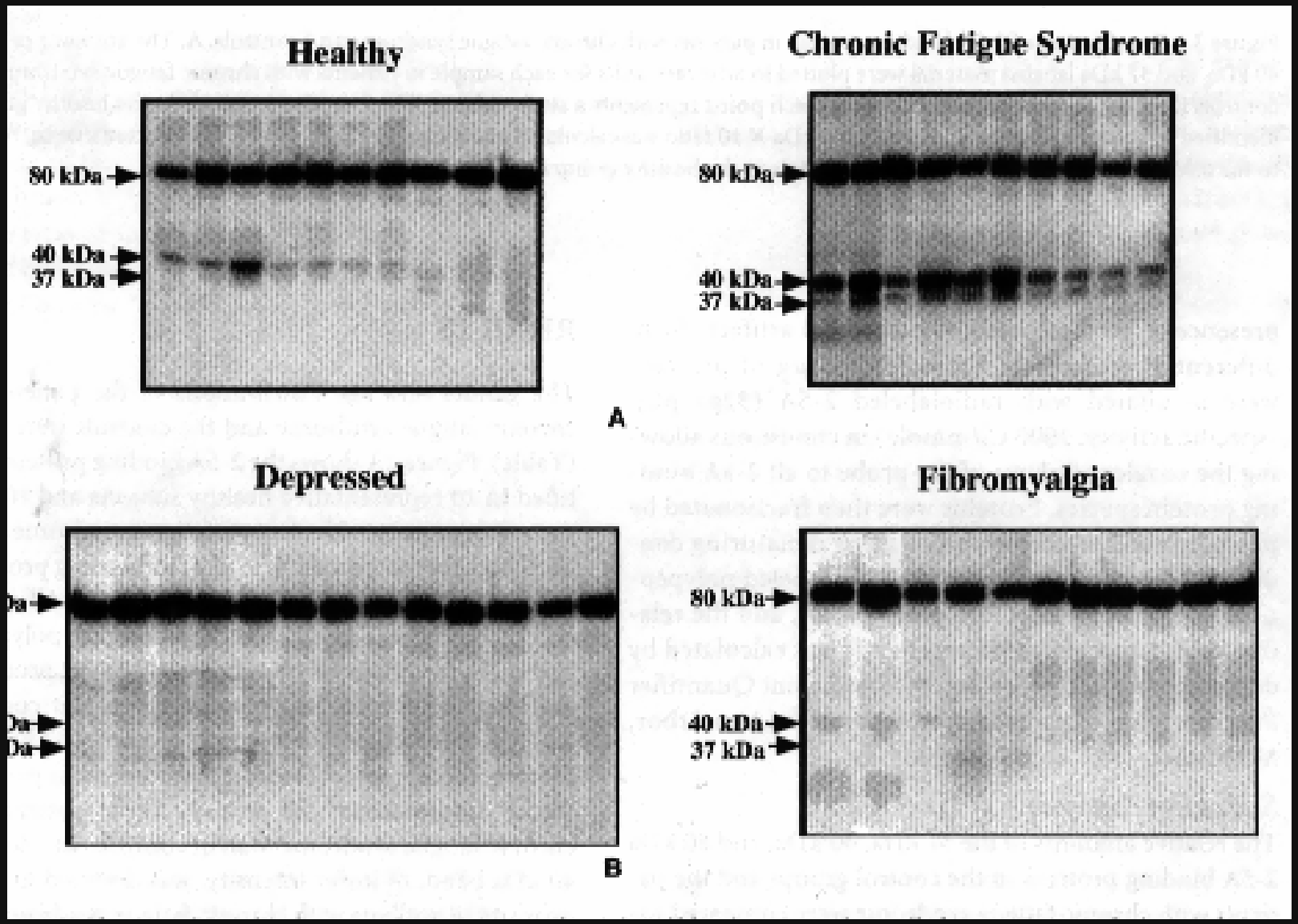


Cuts cellular RNA which increases immune cells suicide rate and opens the door to opportunistic infections

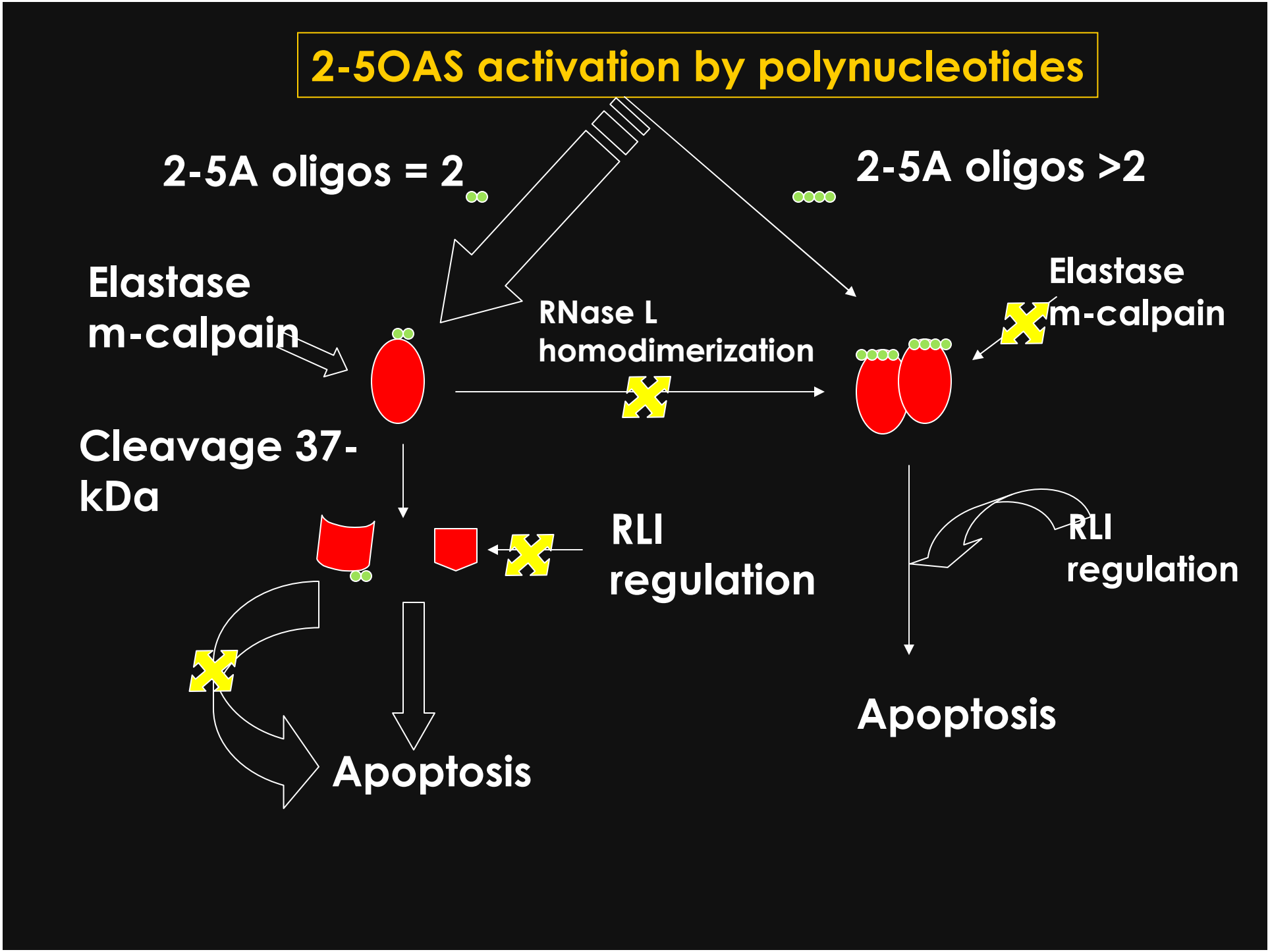


Dysregulate ion channels in many cell types which results in:

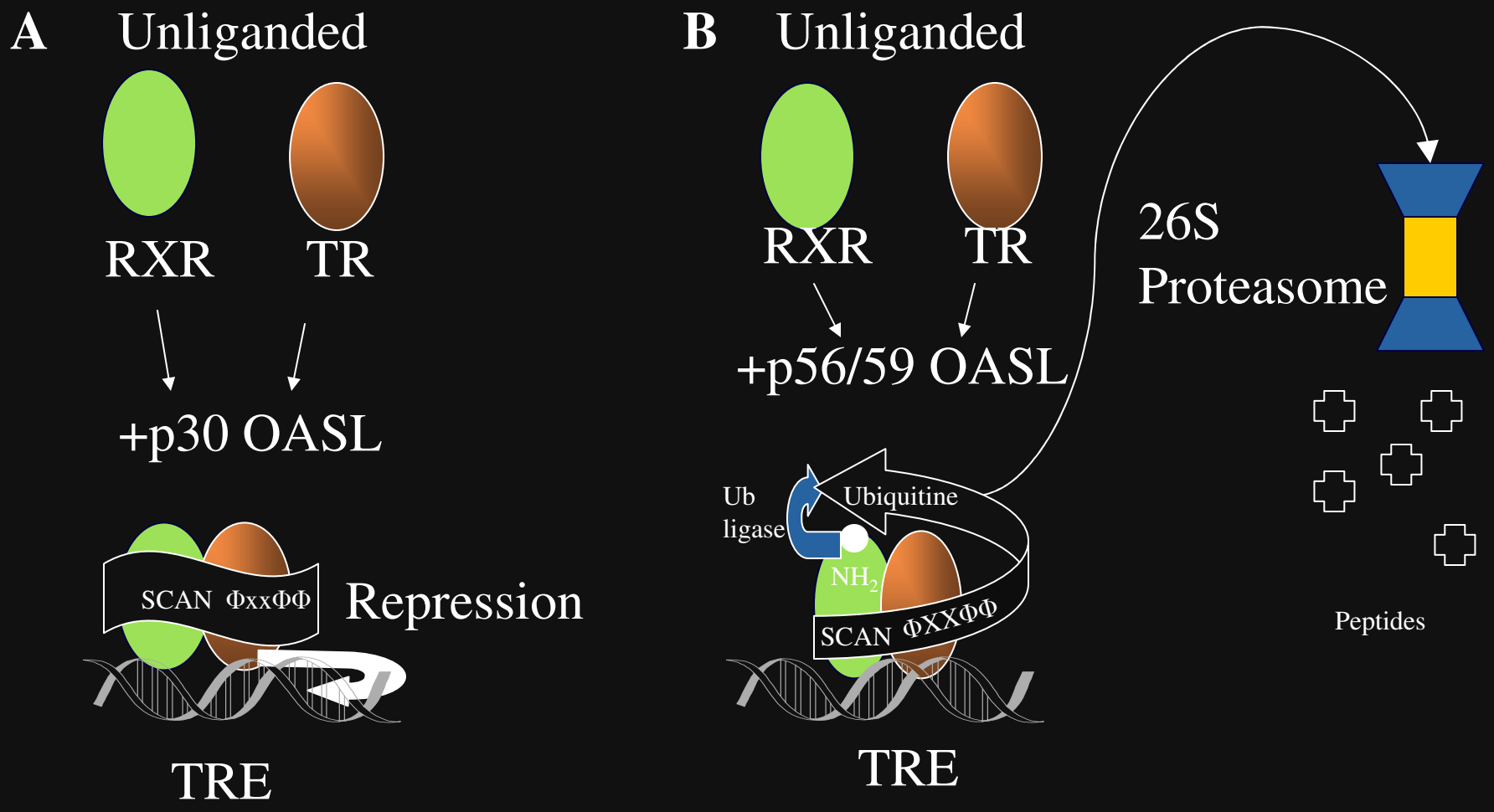
- Unexplained sweats
- Transient hypoglycemia
- Reduction in pain sensitivity threshold
- Depression
- Visual problems
- Hypersensitivity to toxic chemicals



A 37kDa 2-5A binding protein as a potential biochemical marker for Chronic Fatigue Syndrome. Am J Med. 2000; 108: 99-105.

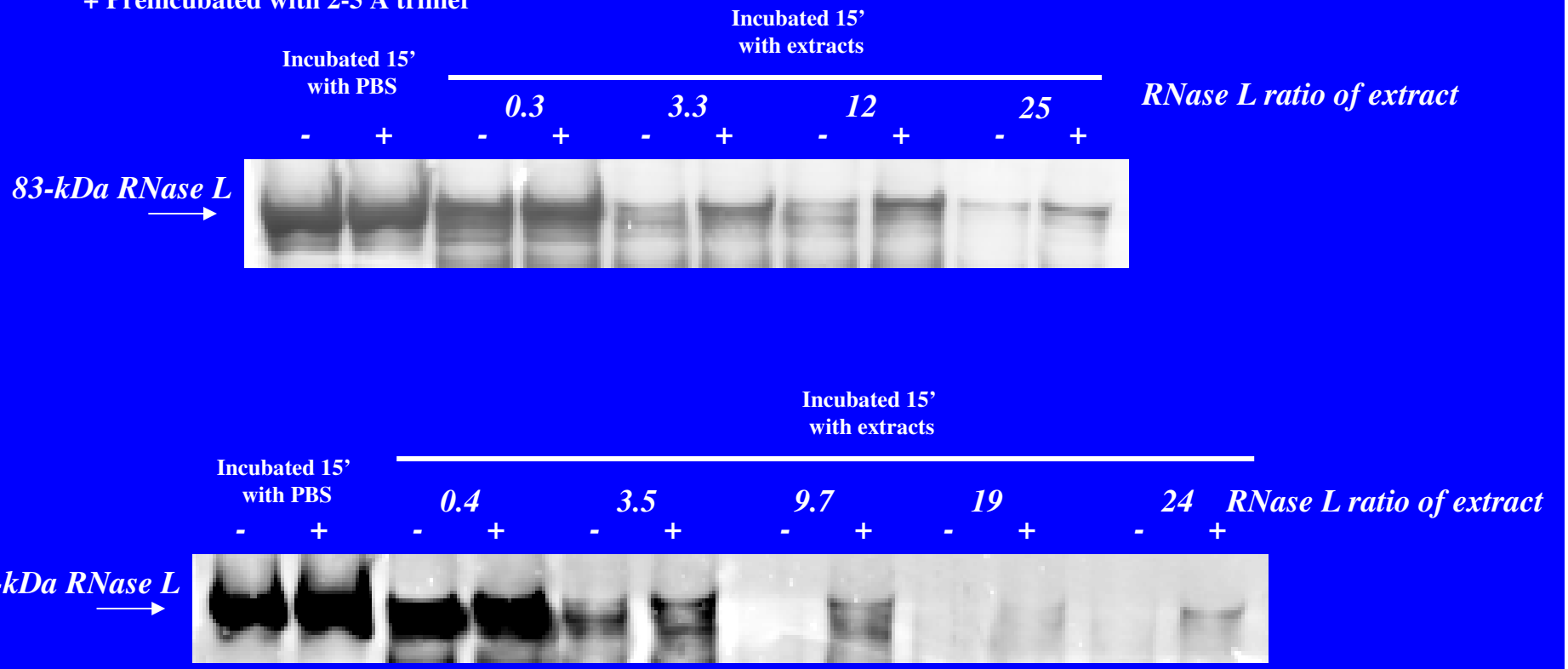

2-5OAS activation by polynucleotides
2-5A oligos = 2
2-5A oligos >2
Elastase
m-calpain
RNase L
homodimerization
Elastase
m-calpain
Cleavage 37-
kDa
RLI
regulation
RLI
regulation
Apoptosis
Apoptosis

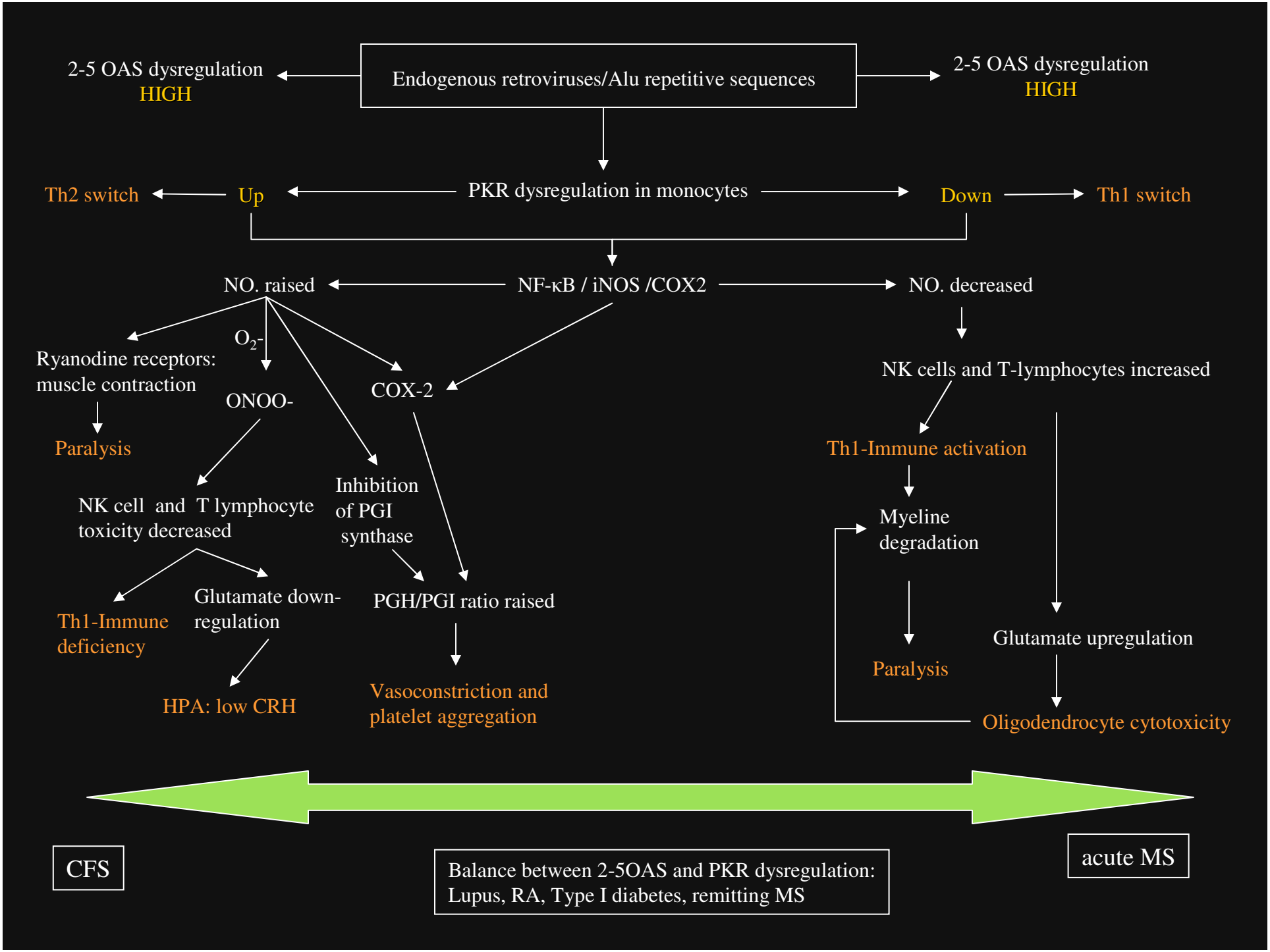
IFN induces 2-5OAS-like proteins which repress or suppress the transactivation by the thyroid receptor. This leads to hypothyroidism (severe fatigue) with normal thyroid hormone levels in blood.



Prior Incubation of Recombinant RNase L with 2-5A trimer prevents its cleavage by PBMC extracts of different ratios

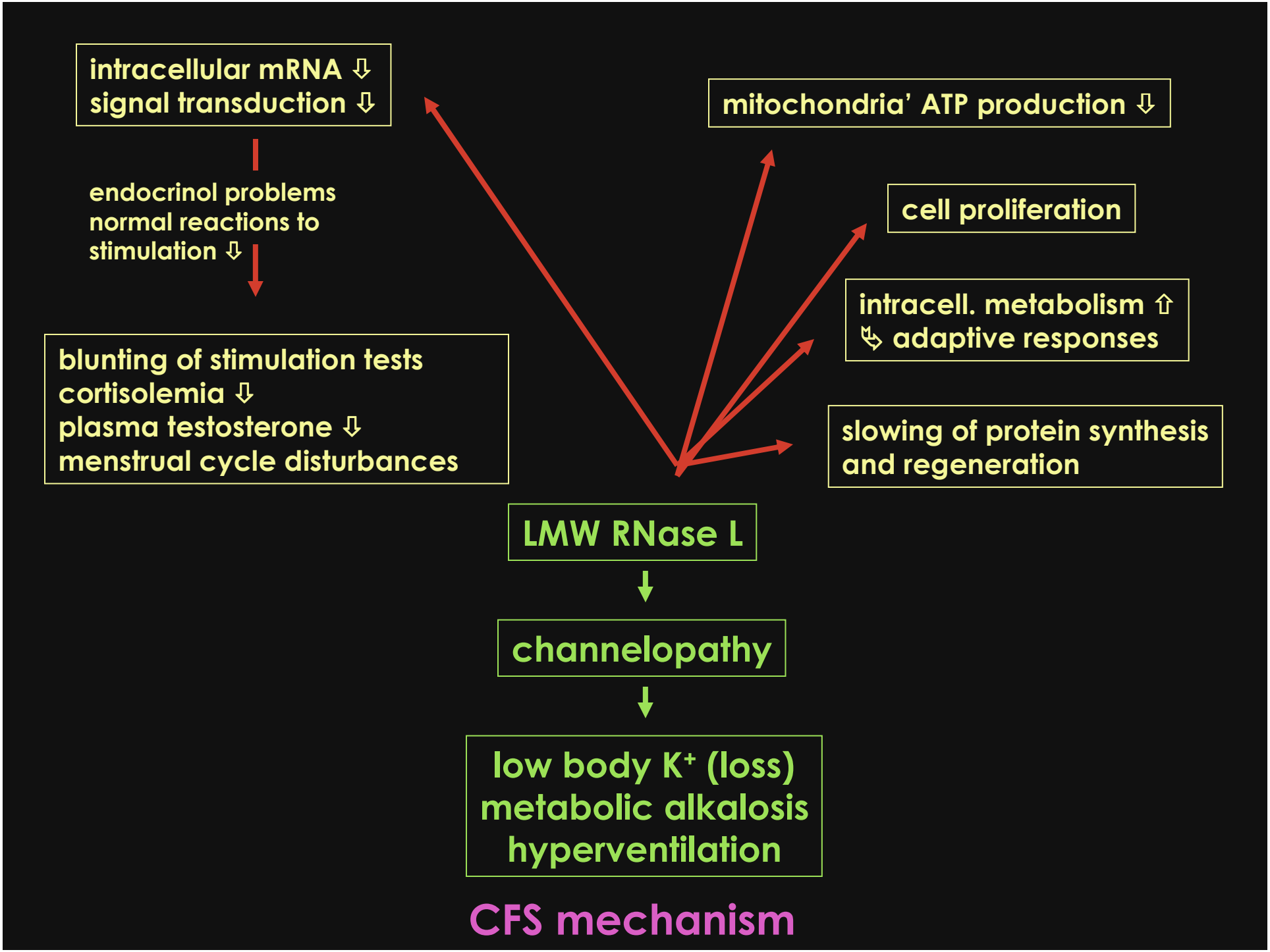
- Preincubated with PBS
+ Preincubated with 2-5 A trimer

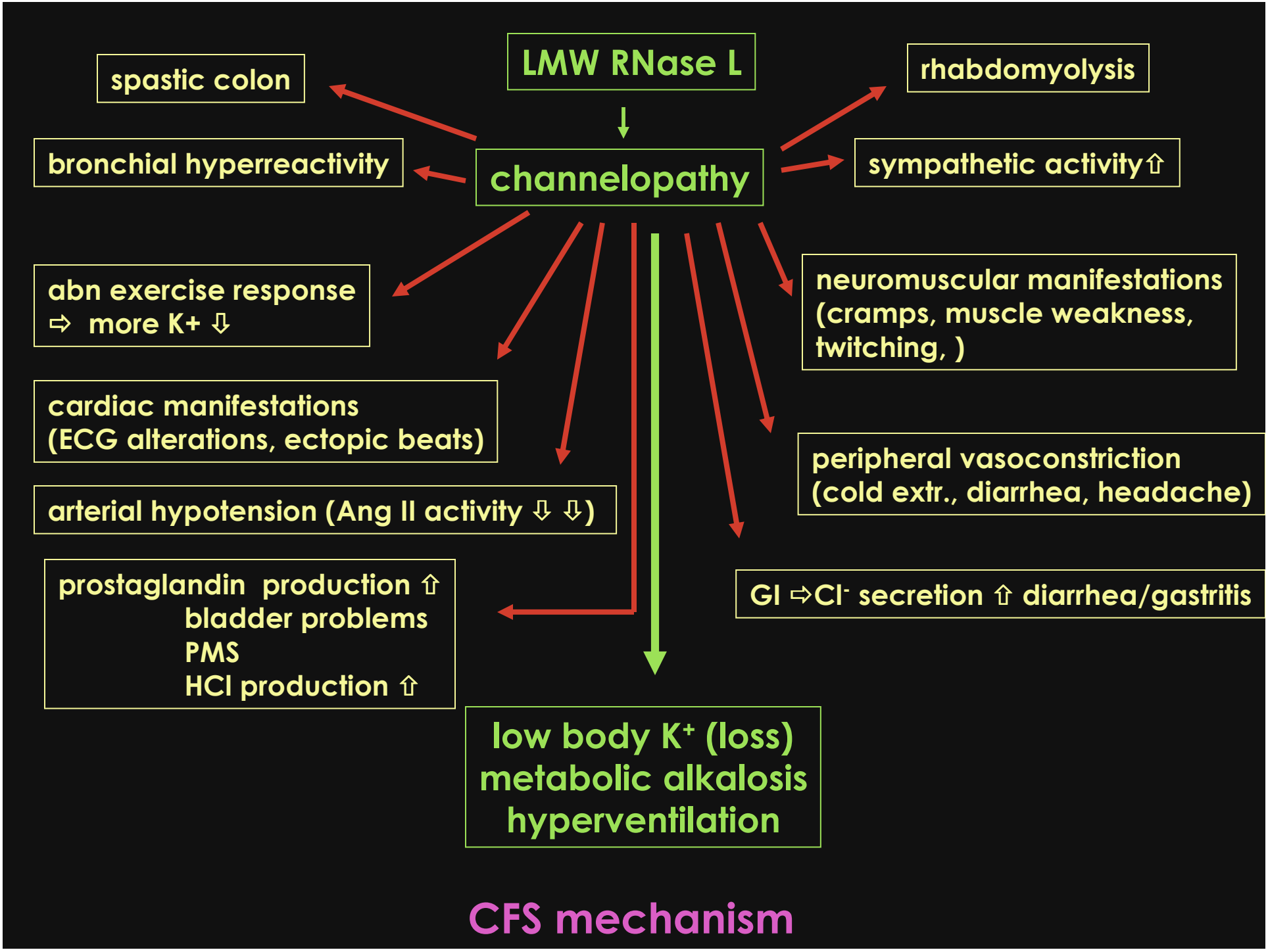



2-5 OAS dysregulation
HIGH
Endogenous retroviruses/Alu repetitive sequences
2-5 OAS dysregulation
HIGH
Th2 switch
Up
PKR dysregulation in monocytes
Down
Th1 switch
NO. raised
NF-κB / iNOS /COX2
NO. decreased
Ryanodine receptors:
muscle contraction
O_2-
COX-2
NK cells and T-lymphocytes increased
Paralysis
ONOO-
Th1-Immune activation
NK cell and T lymphocyte
toxicity decreased
Inhibition
of PGI
synthase
Myeline
degradation
Th1-Immune
deficiency
Glutamate down-
regulation
PGH/PGI ratio raised
Glutamate upregulation
Paralysis
HPA: low CRH
Vasoconstriction and
platelet aggregation
Oligodendrocyte cytotoxicity
CFS
Balance between 2-5OAS and PKR dysregulation:
Lupus, RA, Type I diabetes, remitting MS
acute MS

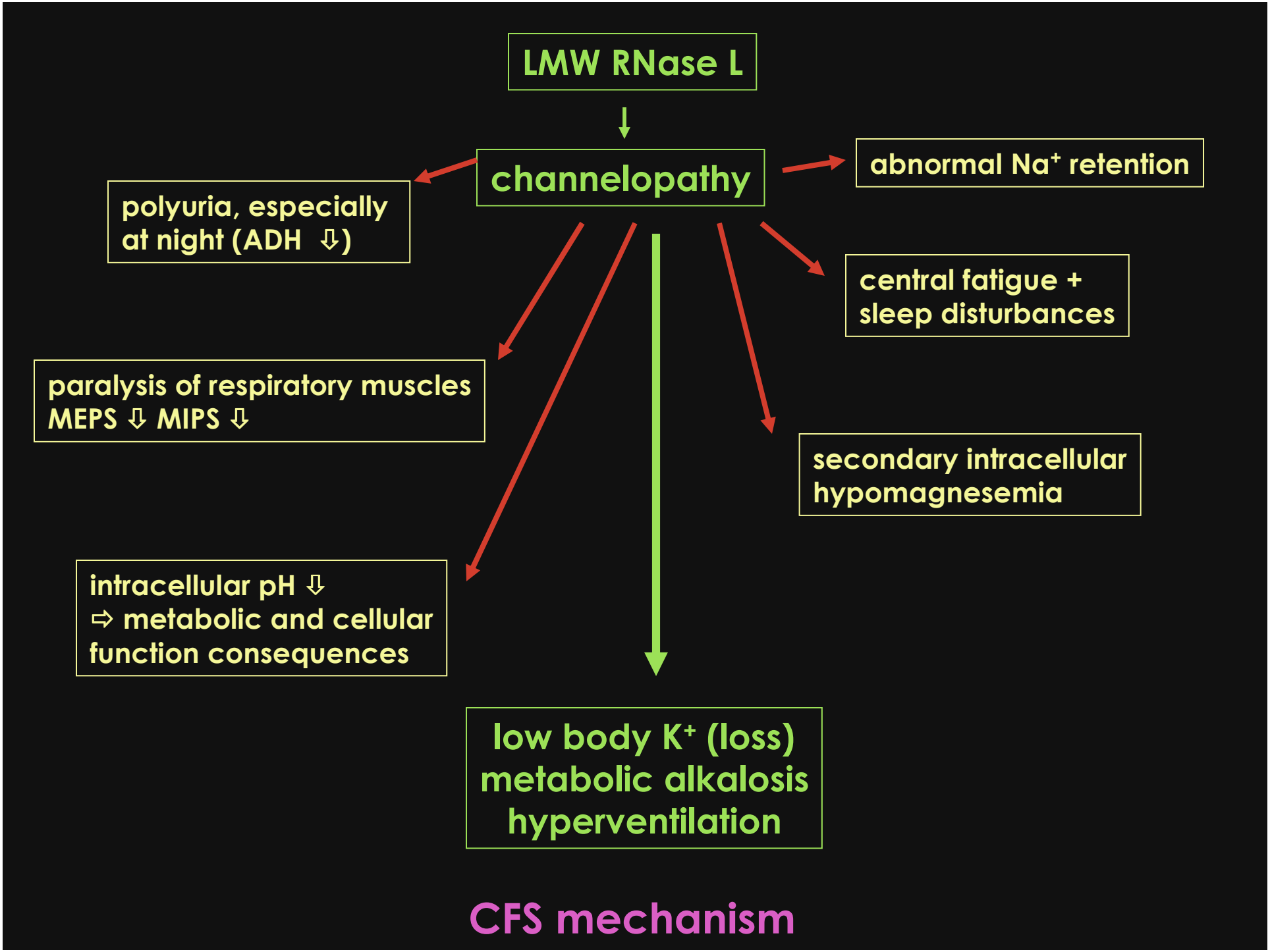
In some cases of innate immunity dysfunction, PKR is simultaneously upregulated (such as in the Chronic fatigue syndrome, CFS), in others (such as acute multiple sclerosis, MS), PKR is downregulated. These examples make the extremes of a dysfunctional array which includes various immune diseases.

Hence, assessing the balance between 2-5OAS and PKR abnormal induction and/or activation or down regulation allows to understand various immune or autoimmune disease manifestations.


intracellular mRNA ⇩
signal transduction ⇩
endocrinol problems
normal reactions to
stimulation ⇩
blunting of stimulation tests
cortisolemia ⇩
plasma testosterone ⇩
menstrual cycle disturbances
mitochondria' ATP production ⇩
cell proliferation
intracell. metabolism ⇧
↳ adaptive responses
slowing of protein synthesis
and regeneration
LMW RNase L
channelopathy
low body K+ (loss)
metabolic alkalosis
hyperventilation
CFS mechanism



CFS mechanism



CFS mechanism

Comparison PCR Mycoplasma CFS/FM patients – healthy/controls

	# positive	(%)
CFS/FM	187 / 272	(68.7)
Controls (1)	1 / 30	(3.3)
Controls (2)	7 / 71	(9.9)

(1) healthy Belgian volunteers

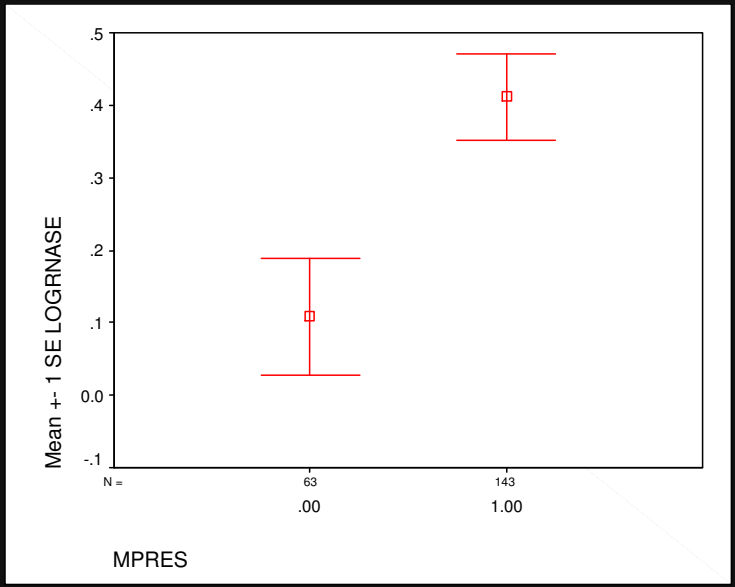
(2) Nasralla, Haier, Nicolson and Nicolson
Int J Med Biol Environ 2000; 28(1): 15-23

RNase L-ratio in Mycoplasma-infected CFS/FM-patients

206 patients

30.6 % No Mycoplasma detected

69.4 % Mycoplasma present



Independent samples t-test → sign different mean values (p = .004)

Error bar plot RNase L after log transformation
.OO = no Mycoplasma; 1.0 = Mycoplasma-infected

Mycoplasma

Antibiotic therapy (36 weeks – 1 year)

Gulf War Syndrome

2 studies: ‘cured’ 78-80%

CFS

3 studies (in total > 700 patients)

⇨ improvement + ‘cured’: 60-60-80%

⇨ cured: 47-50-50%

(2/3 studies not published yet)

Summary of chronic illness patients' antibiotic treatment results

% patients mycoplasma positive or responding to therapy

Reference	A	B	C
GWI (n)	30	170	
Blinded, controlled study	no	no	
Mycoplasma pos patients	47	46	
Clinical Response	ND	ND	
Clinical Recovery	78	80	
CFS/FMS (n)			30
Blinded, controlled study			no
Mycoplasma pos patients			66
Clinical Response			80
Clinical Recovery			50

A: Nicolson & Nicolson (1996); B: Nicolson et al (1998); C: Nicolson (1999)
In: Journal of Chronic Fatigue Syndrome. 6(3/4), 2000, p35.

Treatment of Chlamydia pneumoniae infection in CFS

Treatment schedule:

first day ⇨ Azithromycin (500 mg) orally

day 2-5 ⇨ Azithromycin (250 mg) orally

Improvement by day 3 of treatment, relapsed 12 days later

Second course ⇨ similar to first

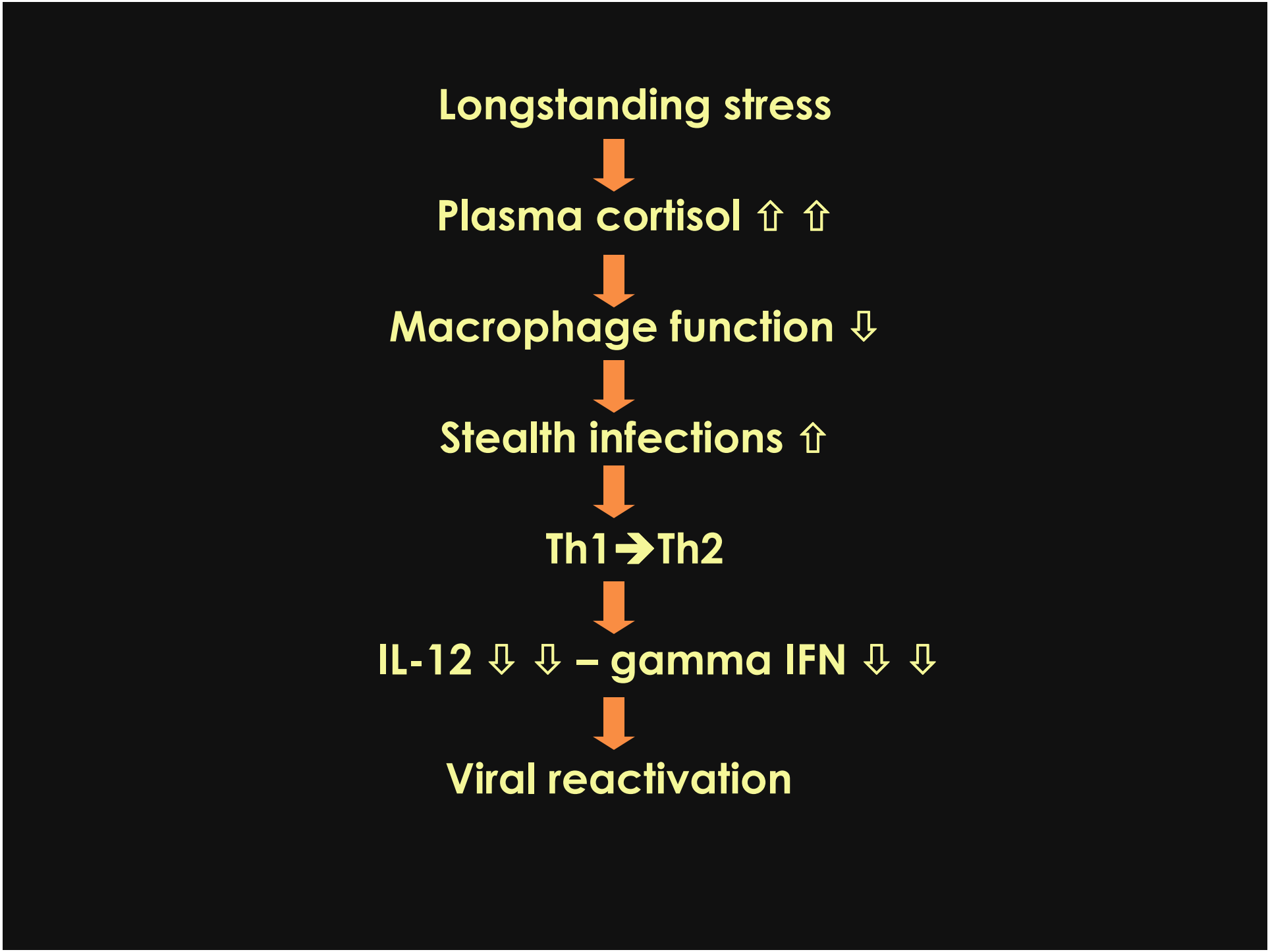
Similar improvement and relapse

Third course ⇨ 30 days Azithromycin (250 mg) orally

complete recovery

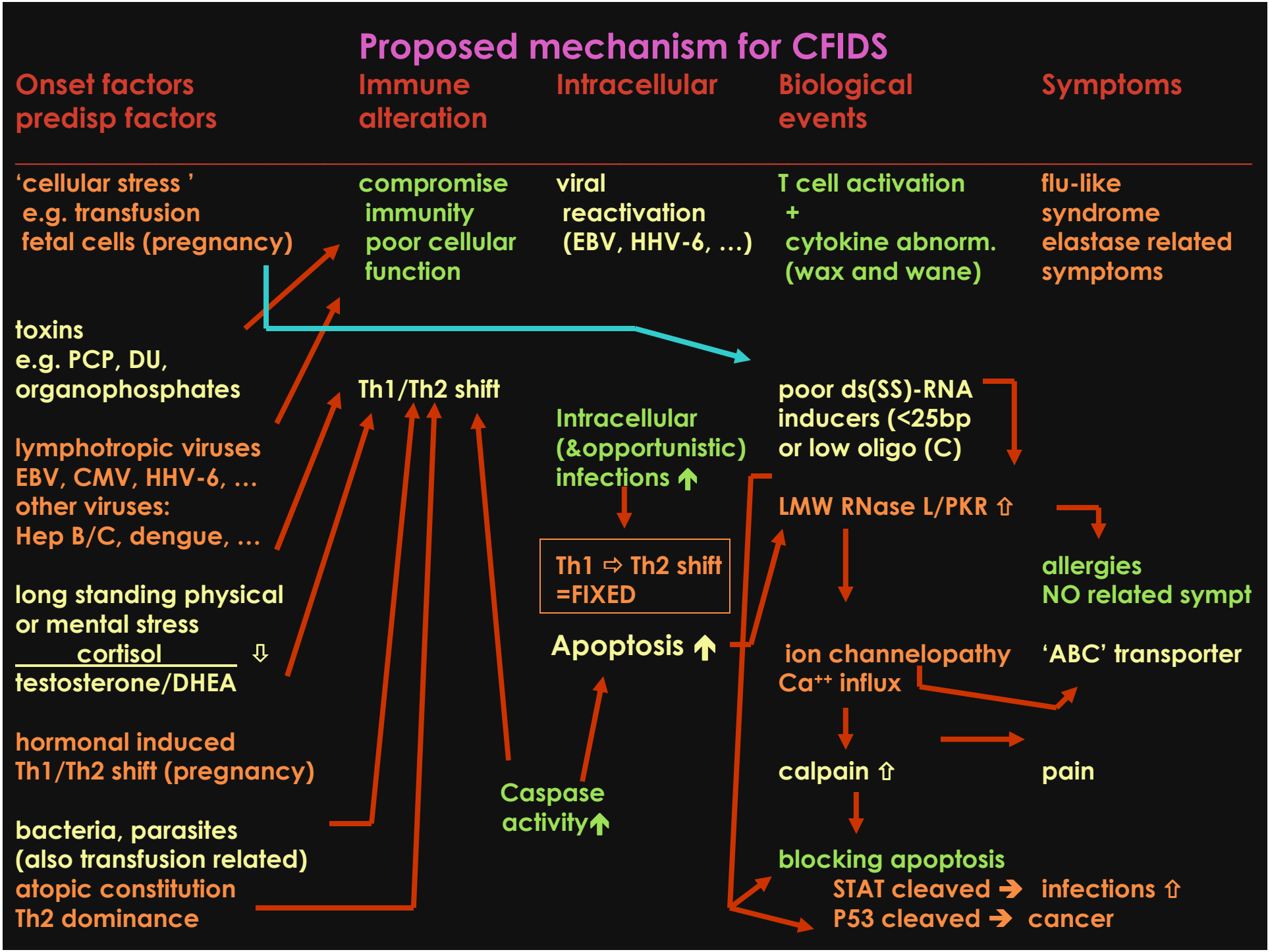
⇨ C. pneumoniae is an uncommon yet treatable cause of chronic fatigue.

Reference: Chronic Chlamydia pneumoniae infection: a treatable cause of Chronic Fatigue Syndrome. Chia et al, Clin Infect Dis. 1999; 29: 452-453.


Longstanding stress
Plasma cortisol ⇧ ⇧
Macrophage function ⇩
Stealth infections ⇧
Th1→Th2
IL-12 ⇩ ⇩ – gamma IFN ⇩ ⇩
Viral reactivation

Predisposing factors

- Celllular stress ⇨ foetal cells
  ⇨ transfusion
- Toxins: PCP, DU, organophosphates, mycotoxins, heavy metals…
- Lymphotropic viruses: EBV, CMV, HHV-6, Dengue, …
- Long-standing physical and/or mental stress ⇨ cortisol/testosterone ⇩ + DHEA ⇩
- Hormonal changes (estrogens) 'Th1/Th2 shift'
- Bacteria, parasites ⇨ Th2 induction
- Leaky gut syndrome
- Genetic predisposition
  - ⇨ allergy
  - ⇨ Th2 predominance
  - ⇨ other genetic defects


Proposed mechanism for CFIDS
Onset factors predisp factors
Immune alteration
Intracellular
Biological events
Symptoms
'cellular stress '
e.g. transfusion
fetal cells (pregnancy)
compromise immunity
poor cellular function
viral reactivation
(EBV, HHV-6, …)
T cell activation +
cytokine abnorm.
(wax and wane)
flu-like syndrome
elastase related symptoms
toxins
e.g. PCP, DU, organophosphates
Th1/Th2 shift
poor ds(SS)-RNA inducers (<25bp or low oligo (C)
lymphotropic viruses
EBV, CMV, HHV-6, …
other viruses:
Hep B/C, dengue, …
Intracellular (&opportunistic) infections ↑
LMW RNase L/PKR ⇧
long standing physical or mental stress
cortisol ⇩
testosterone/DHEA
Th1 ⇨ Th2 shift =FIXED
allergies
NO related sympt
Apoptosis ↑
ion channelopathy
Ca++ influx
'ABC' transporter
hormonal induced
Th1/Th2 shift (pregnancy)
calpain ⇧
pain
Caspase activity↑
bacteria, parasites
(also transfusion related)
atopic constitution
Th2 dominance
blocking apoptosis
STAT cleaved ➔ infections ⇧
P53 cleaved ➔ cancer

Therapeutic strategies

Goal

- Restoration of ⇨ immune competence (macrophage activity, …)
  ⇨ Th1/Th2 ratio with ⇩ reactivation herpes viruses
- Elimination / decrease in load of certain micro-organisms
- Restoration of hormonal balance
- Decreasing heavy metal load
- Metal allergies
- Decreasing PKR activity