

Overlap syndromes

Mixed connective tissue disease (MCTD)

Undifferentiated connective tissue disease (UCTD)

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Overlap syndromes, MCTD, UCTD

- Definition
- Historical perspective
- Classification Criteria
- Autoimmunity and immune pathogenesis

Definition

➤ UCTD:

Presence of clinical and serological manifestations suggestive of systemic autoimmune diseases but not fulfilling the classification criteria for defined CTD.

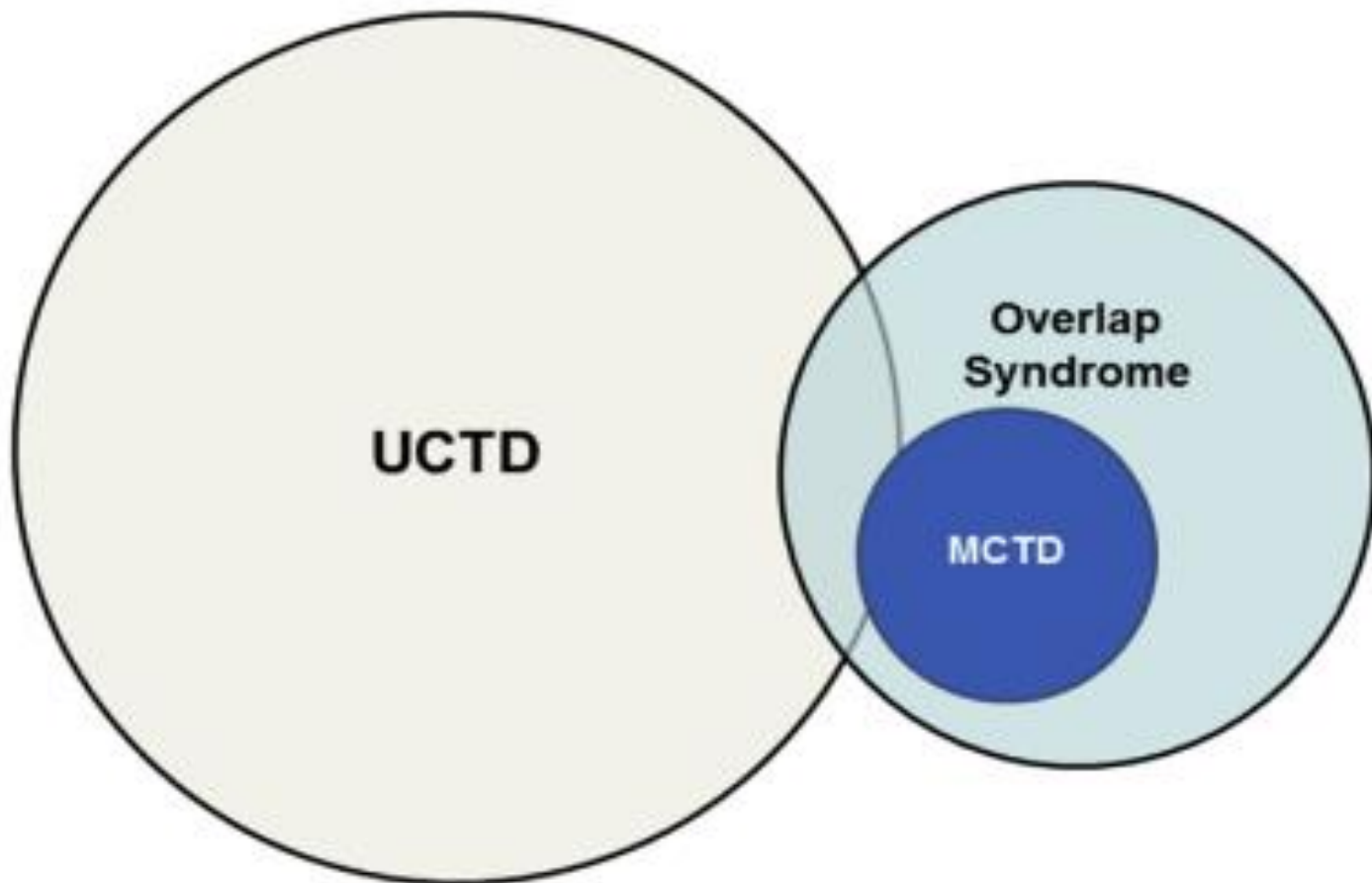
➤ Overlap Syndrome:

- a) A patient who has features of two or more distinctly recognizable rheumatic diseases such as RA and SLE(**rhupus**).
- b) To describe the predominance of selected clinical features, such as ILD or myopathy (i.e., myositis-pulmonary overlap), in patients with another recognizable rheumatic disease.

➤ MCTD:

Overlapping features of SSc, SLE, PM/DM and high levels of anti-U1RNP.

Definition



UCTD

- It is estimated that up to 50% of patients with CTDs have unclassifiable profile at disease onset.

Alarcon . J Rheumatol 1991

- Patients with **clinical** and **serological** manifestations strongly suggesting a connective tissue disease but **not fulfilling** any of existing classification criteria for defined CTD.
- Leroy proposed the concept of UCTD to define early phases of CTD (1980).
- Most of patients are female in 3rd-4rd decade of life.

UCTD

➤ Clinical features:

arthralgia
mild Raynaud's phenomenon
non erosive arthritis
leukopenia
anemia
xerophthalmia
xerostomia
photosensitivity
serositis
malar rash
oral aphthosis
thrombocytopenia

UCTD

- Life threatening conditions and severe organ involvements (such as renal or neurological) are only occasionally reported.
Mosca and etal. Rheumatol 2013
- But a moderate to severe interstitial lung involvement (ILD) can be also observed.
- Up to 88% of patients with idiopathic nonspecific interstitial pneumonia meet the criteria for UCTD.
Kinder and etal. LUNG 2010
- Pregnancy might driver disease exacerbation or evolution.
Gastellino and etal. Lupus 2011

UCTD

➤ Stable or evolving UCTD:

- 70% of patients of UCTD will remain as such over time.
- 30% will develop a defined CTD over the follow up.
- the evolution occurs in the majority of cases within the first years of disease (3-5 years).

UCTD

- Among the UCTD patients who evolve to CTDs, **SLE** is the most frequently reported diagnosis (**20-60%**).
- Although an evolution to other CTDs such as systemic sclerosis (**SSc**), sjogren's syndrome (**SS**), Mixed connective tissue disease (**MCTD**), polydermatomyositis (**PM/DM**), rheumatoid arthritis (**RA**) has been described.

Mosca and etal. J of Autoimunity 2014

➤ Prognostic factors for evolution into CTDs:

the presence of the multiple autoantibodies specificities

anti-dsDNA, anti-Sm, anti-centromere Ab

homogeneous ANA pattern

puffy finger

Gotttron's papules

discoid lupus

giant loops on capillaroscopy

high Th17/Treg

UCTD

➤ Preliminary criteria:

1. Signs and symptoms suggestive of a connective tissue disease, but not fulfilling criteria for defined CTDs.
2. Positive antinuclear antibodies.
3. A disease duration of at least 3 years.

Mosca and etal. Clin Exp Rheumatol 1999

- If the disease duration is less than 3 years patients may be defined as having an early UCTD (EUCTD).

MCTD

- In 1972, Sharp et al. described a new autoimmune rheumatic disease that they called MCTD.
- Characterized by overlapping features of SSc, SLE, PM/DM, high levels of anti-U1 RNP and low steroid requirements with good prognosis.
- More common in women (11-16/1 female-to-male ratio).
- 2.7-3.8 per 100,000 prevalence.

MCTD

➤ Four sets of classification criteria for MCTD have been published.

1. Sharp (1987)
2. Alarcon-Segovia (1987)
3. Kasukawa (1987)
4. Kahn (1991)

Sharp criteria

Major criteria

1. Myositis
2. Pulmonary involvement:
 - a. Diffuse capacity <70% of normal
 - b. pulmonary hypertension
 - c. Proliferative vascular lesion on lung biopsy
3. Raynaud's phenomenon or esophageal hypomotility
4. Swollen hands
5. Anti-ENA > 1:10.000 and anti- U1 RNP positive and anti-Sm negative

Minor criteria

1. Alopecia
2. Leukopenia
3. Anemia
4. Pleuritis
5. Pericarditis
6. Arthritis
7. Trigeminal neuropathy
8. Malar rash
9. Thrombocytopenia
10. Mild myositis
11. History of swollen hands

Requirements for diagnosis

At least **four major** criteria **plus anti-U1 RNP** titer of at least 1:4000. Exclusion criteria: anti-Sm antibody positivity.
two major criteria from 1, 2 and 3 plus 2 minor criteria plus anti-U1RNP titer of at least 1:1000

- Sensitivity: 42%
- Specificity: 87.7%

Kasukawa

Common Symptoms

1. Raynaud's phenomenon
 2. Swollen fingers Or hands
- Anti-RNP Ab
Positive

Mixed symptoms

1. SLE-like symptoms:
 - a. Polyarthritis
 - b. Lymphadenopathy
 - c. Facial erythema
 - d. Pericarditis or Pleuritis
 - e. Leuko-thrombocytopenia
2. SSc-like findings:
 - a. Sclerodactyly
 - b. Pulmonary fibrosis
resrtictive changes of lung
or reduce diffusion capacity
 - c. Hypomotility or dilatation
of esophagus
3. PM-like findings:
 - a. Muscle weakness
 - b. elevated CPK
 - c. Myogenic pattern on EMG

Requirement for diagnosis

At least 1 of common symptoms
plus positive for anti-RNP plus
1 more of the mixed symptoms in at least
2 of the 3 disease categories.

➤ Specificity: 99.8% Sensitivity: 75%

Oscar-Danilo, et al. Best Practice & Research Clinical Rheumatology 2012

Alarcon-Segovia

Serological

Anti-RNP
titer $\geq 1:1.600$

Clinical

1. Swollen hands
2. Synovitis
3. Myositis
4. Raynaud's phenomenon
5. Acrosclerosis

Requirements for diagnosis

Serological criteria plus at least three clinical criteria included either synovitis or myositis

- Specificity: 86.2%
- Sensitivity: 62.5%

Oscar-Danilo, et al. Best Practice & Research Clinical Rheumatology 2012

Kahn

Serological

Presence of
high titer
Anti-RNP
Corresponding
To speckled
ANA at titer
 $\geq 1: 1200$

Clinical criteria

- a. Raynaud's phenomenon
- b. Synovitis
- c. myositis
- d. swollen fingers

Requirements for diagnosis

Serological criteria plus Raynaud's phenomenon and at least two of the three following signs (synovitis, myositis and swollen fingers)

➤ Sensitivity: 63% Specificity: 86%

Oscar-Danilo, et al. Best Practice & Research Clinical Rheumatology 2012

Immune pathogenesis of MCTD

➤ Genetic Factors:

- The frequency of HLA-DR4 is increased in patients compared to healthy controls.
- Polymorphism in chromosome 3.
- HLA-DR5 and HLA-DR3 have a negative association.

Hofman, et al. clinical immunology 2008

Immune pathogenesis of MCTD

➤ Environmental factors:

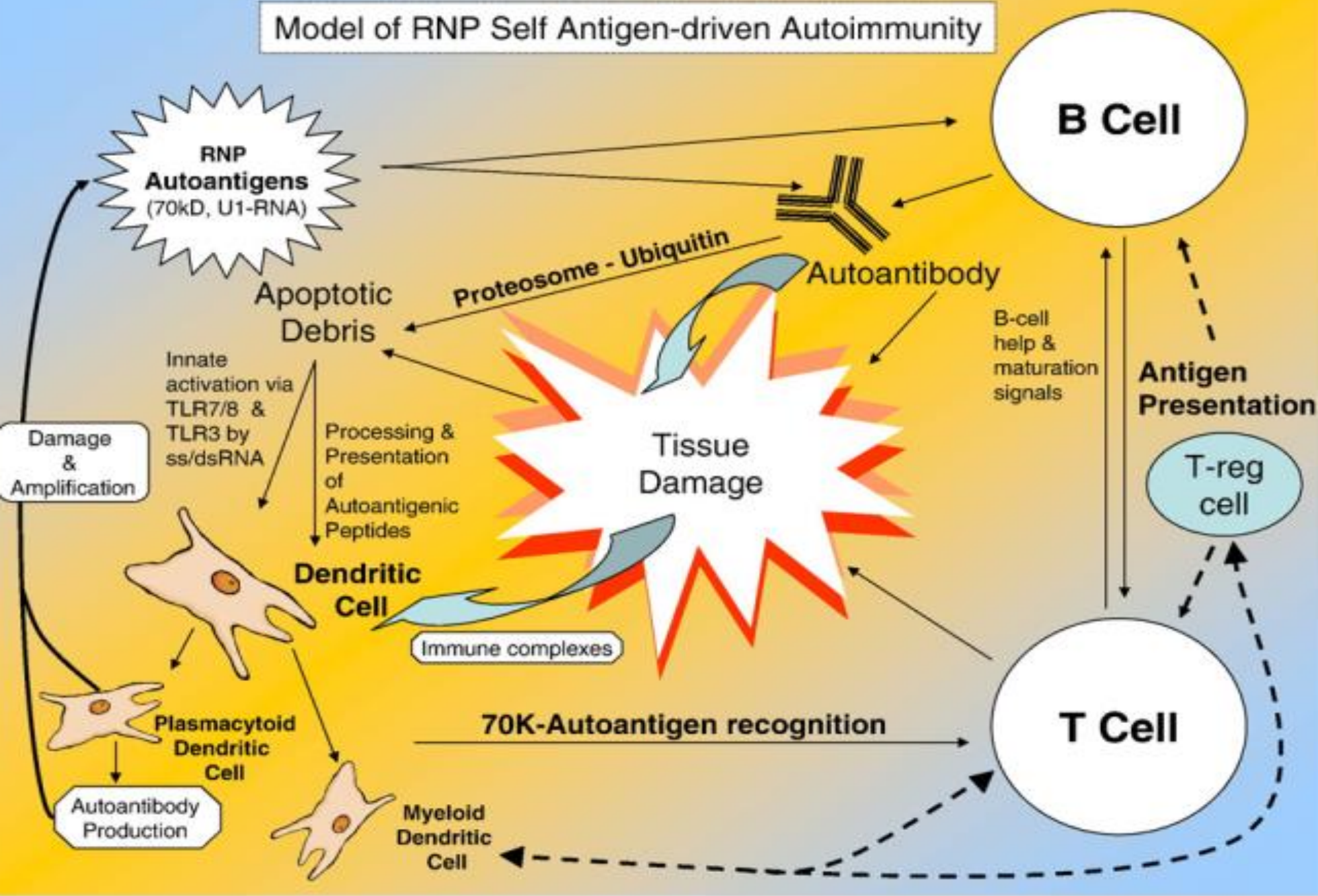
- Female sex hormones
- Epstein-Bar virus
- Retrovirus
- Cytomegalovirus
- Vinyl chloride
- Silica

Hofman, et al. clinical immunology 2008

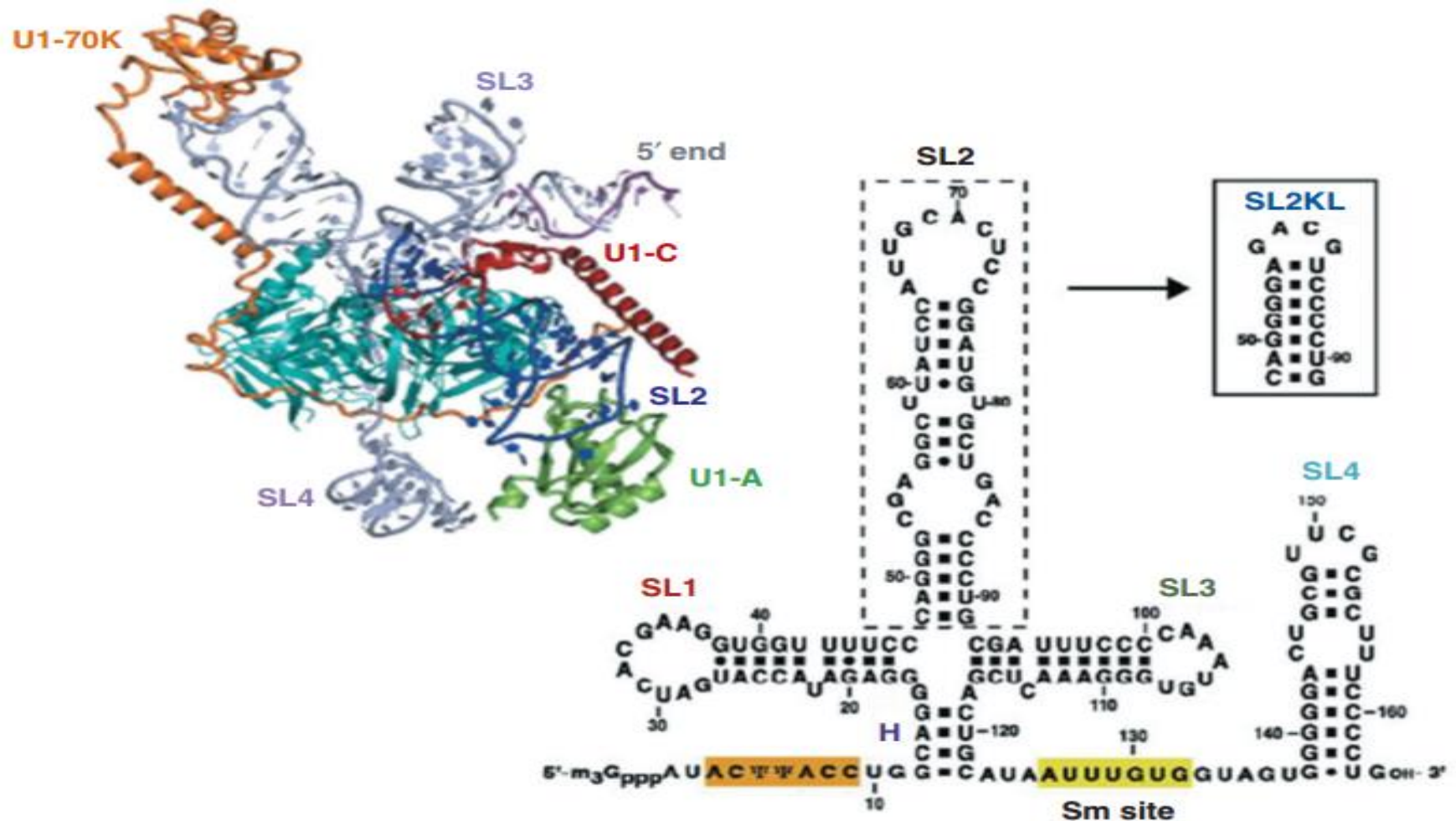
Immune pathogenesis of MCTD

- Autoantigen-structural modifications that may influence immune tolerance.
- Innate immune signaling and loss of immunologic tolerance.
- Adaptive immune system:
 - CD4+ T cell
 - CD8+ T cell
 - T regulatory
 - B cell
- Tissue injury:
 - One of the primary targets of tissue injury is the **vascular endothelium**.
 - A bland **intimal proliferation** and **medial hypertrophy** affects medium and small size vessels.

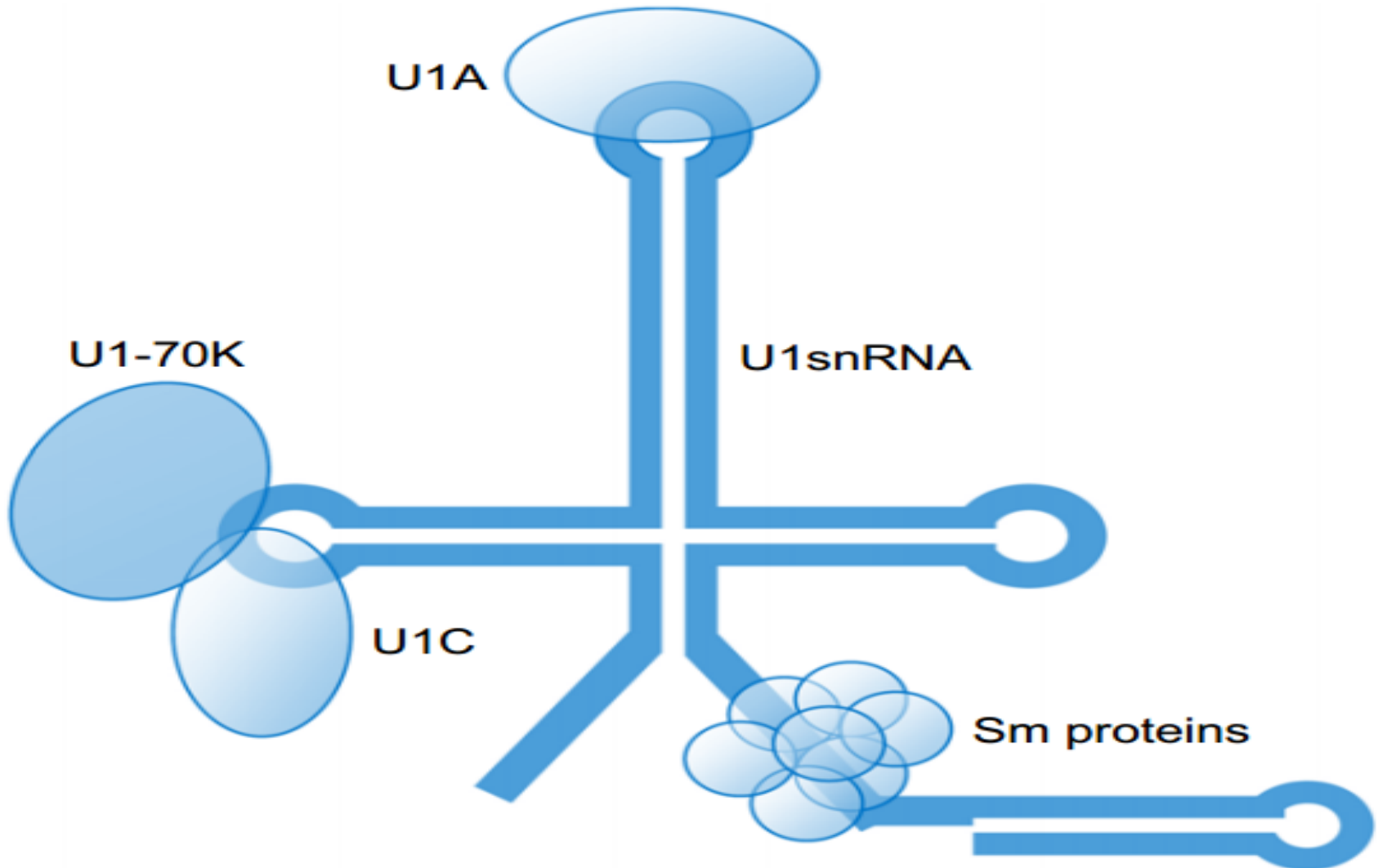
Model of RNP Self Antigen-driven Autoimmunity



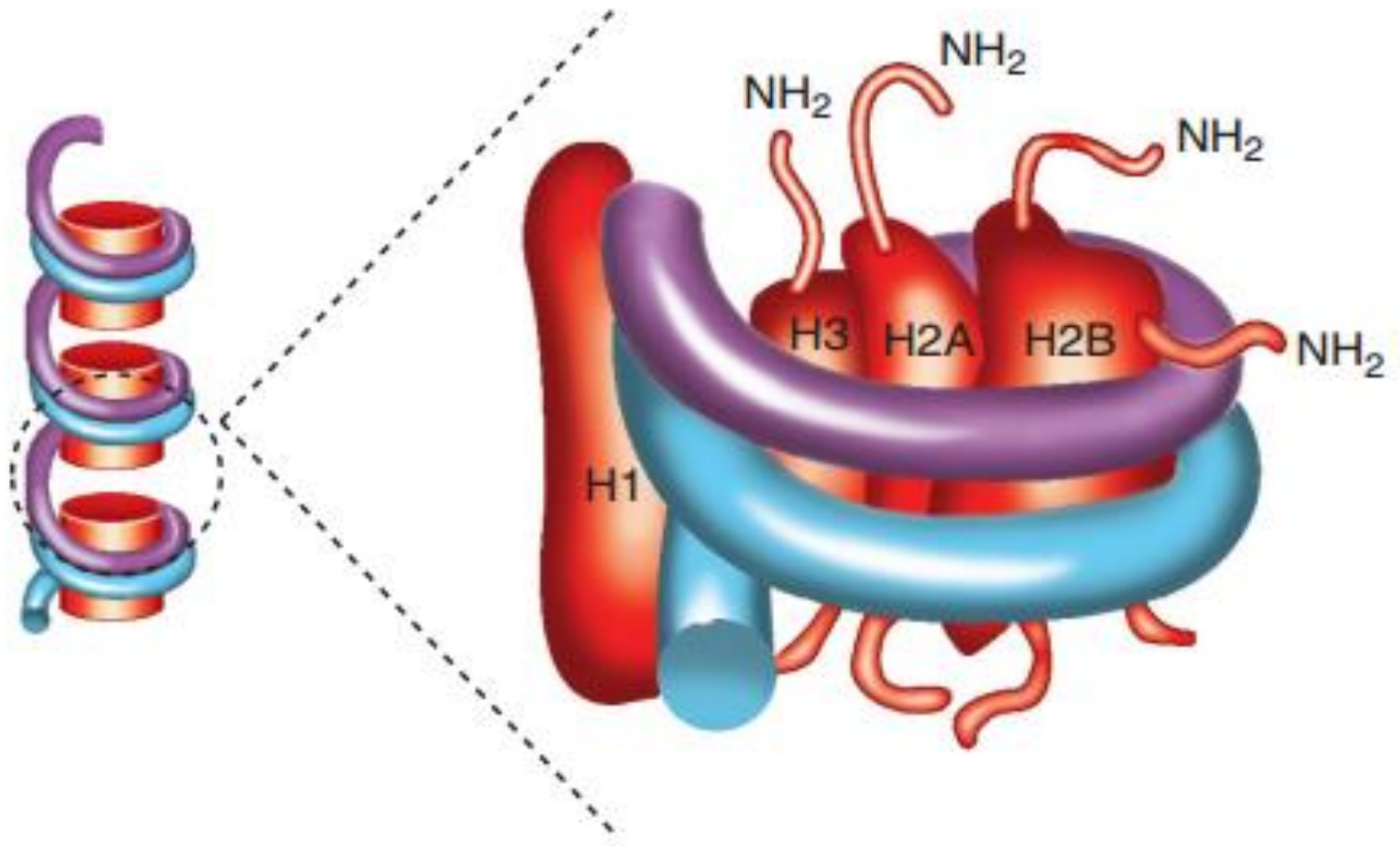
Autoimmunity to spliceosomal components



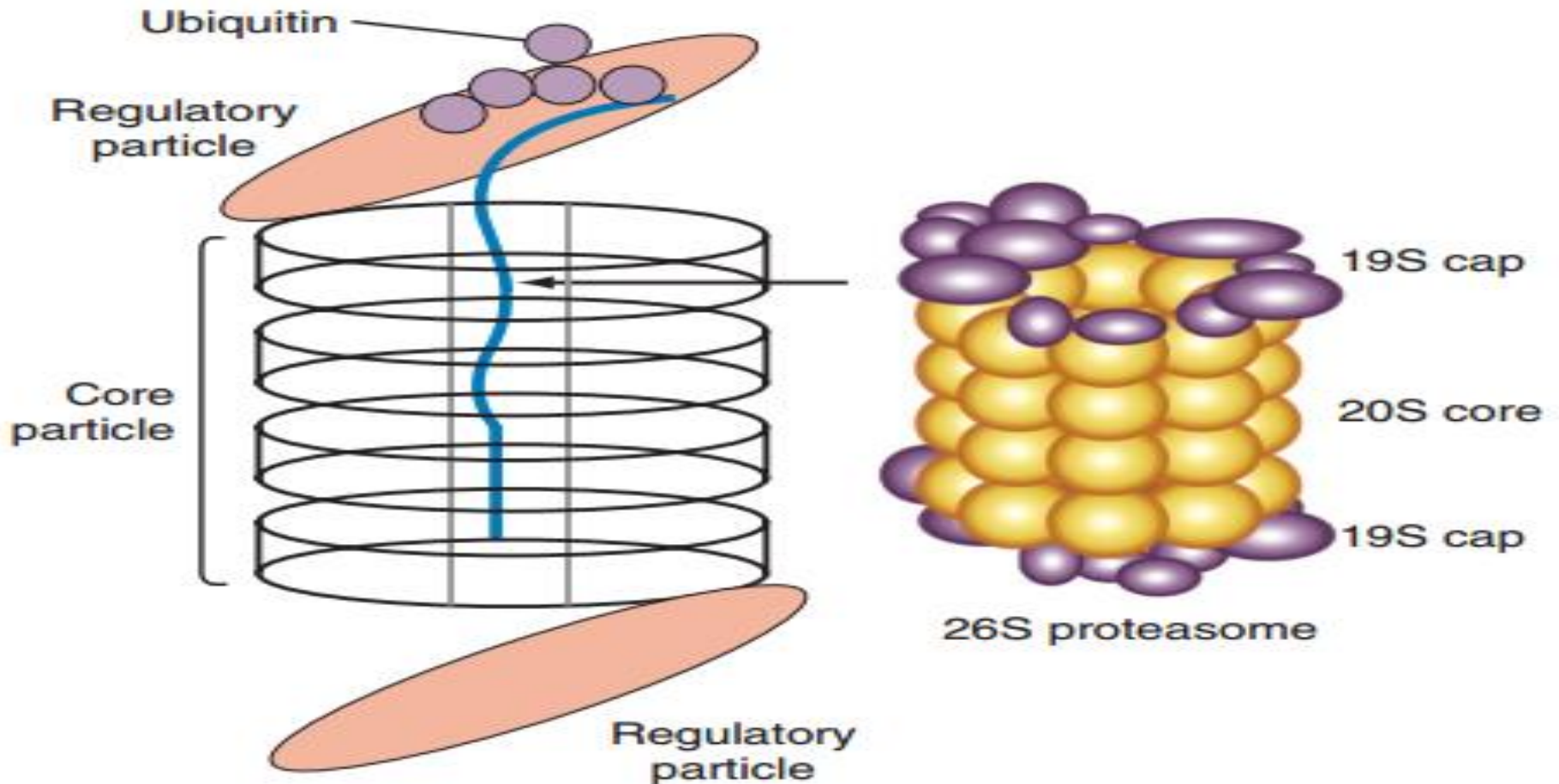
Small nuclear (snRNP) molecule



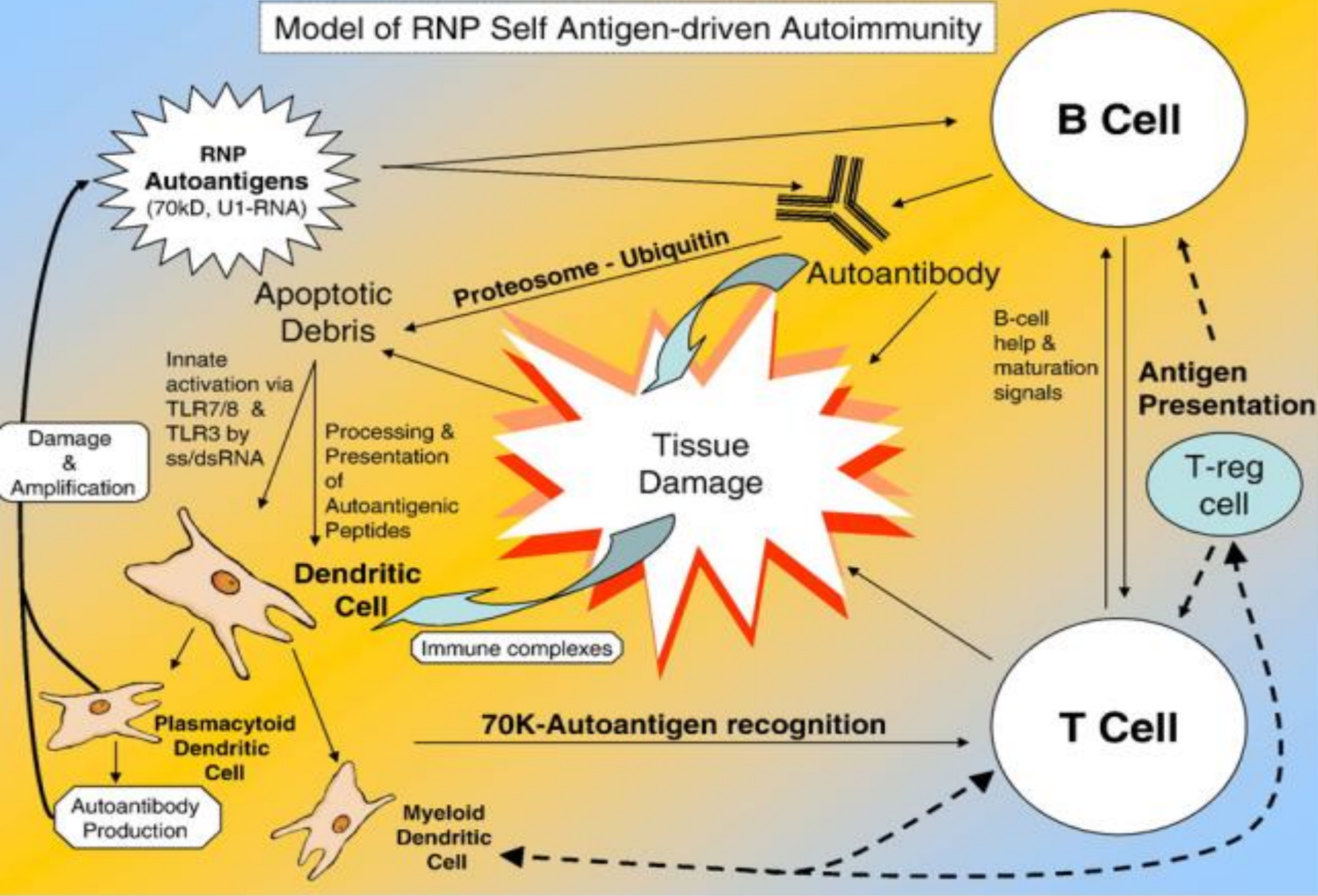
Autoimmunity to Nucleosomal component



Autoimmunity to Proteasomal components



Model of RNP Self Antigen-driven Autoimmunity





Thank you ever so much for your attention