

# Knowledge Systematization of Cellular Senescence Process by Homeostasis Imbalance Process Ontology

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## BACKGROUND

- As explained in several textbooks, aging is **not a disease**, but a **risk factor**.
  - Can we regulate aging?
- Aging has already begun from birth, and senescence is repeated at the cell level throughout our life.
- Recent studies suggest cellular senescence plays both suppressor and inducer in cancer.
  - What mechanisms underlie aging?

## APPROACH

- Develop an ontology: **Homeostasis Imbalance Process Ontology (HoIP)**

<https://bioportal.bioontology.org/ontologies/HOIP>  
cellular senescence course:  
[http://purl.bioontology.org/ontology/HOIP/HOIP\\_0060024](http://purl.bioontology.org/ontology/HOIP/HOIP_0060024)

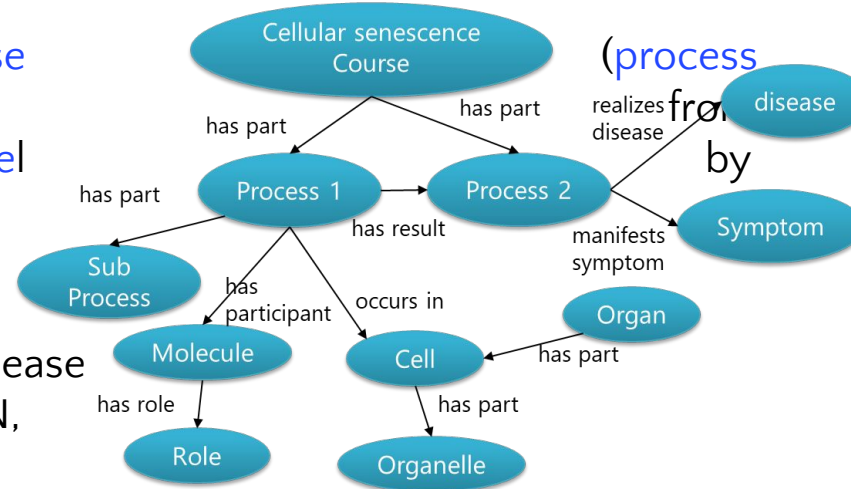
## OBJECTIVES

- To systematize knowledge of the cellular senescence processes based on an ontological approach.
- To clarify how cellular senescence develops into pathological manifestations, symptoms, and age-related diseases.

## Challenge: coping with the granularity from micro to macro levels

How do we represent the granularity of a wide variety of phenomena from molecule to cell levels?

- Describe a mechanism as a **course series**) for phenomena spanning **cell to disease at an organism level** manual annotation
- Unify the representation of functioning process, structure, molecule, role, symptom, and disease by referring to BFO, GO, UBERON, HP, SYMP, PRO, and ChEBI



label [type: xsd:string]  
senescence-associated secretory phenotype (SASP) secretion

definition [type: xsd:string]  
The release of the senescence-associated secretory phenotype from a cell.  
This entity is a specific course-dependent process. The course of cellular senescence

SubClass Of +

- 'has agent' some 'senescent cell'
- 'has context' only 'cellular senescence course'
- 'has output' some 'C-C motif chemokine 2 (human)'
- 'has output' some 'interleukin-6 (human)'
- 'has output' some 'interleukin-8 (human)'
- 'has output' some 'matrix metalloproteinase'
- 'has output' some hCXCL1
- 'has output' some serpin
- 'has part' some 'type I interferon production [cellular senescence]'
- 'has result' some 'chronic inflammation'
- 'has result' some 'fibrosis [cellular senescence]'
- 'has result' some 'hypofunction of keeping stem cell niche [cellular senescence]'
- 'has result' some 'inflammatory cell infiltration [cellular senescence]'
- 'has result' some 'negative regulation of tissue

Process: senescence-associated secretory phenotype (SASP) secretion

Molecules

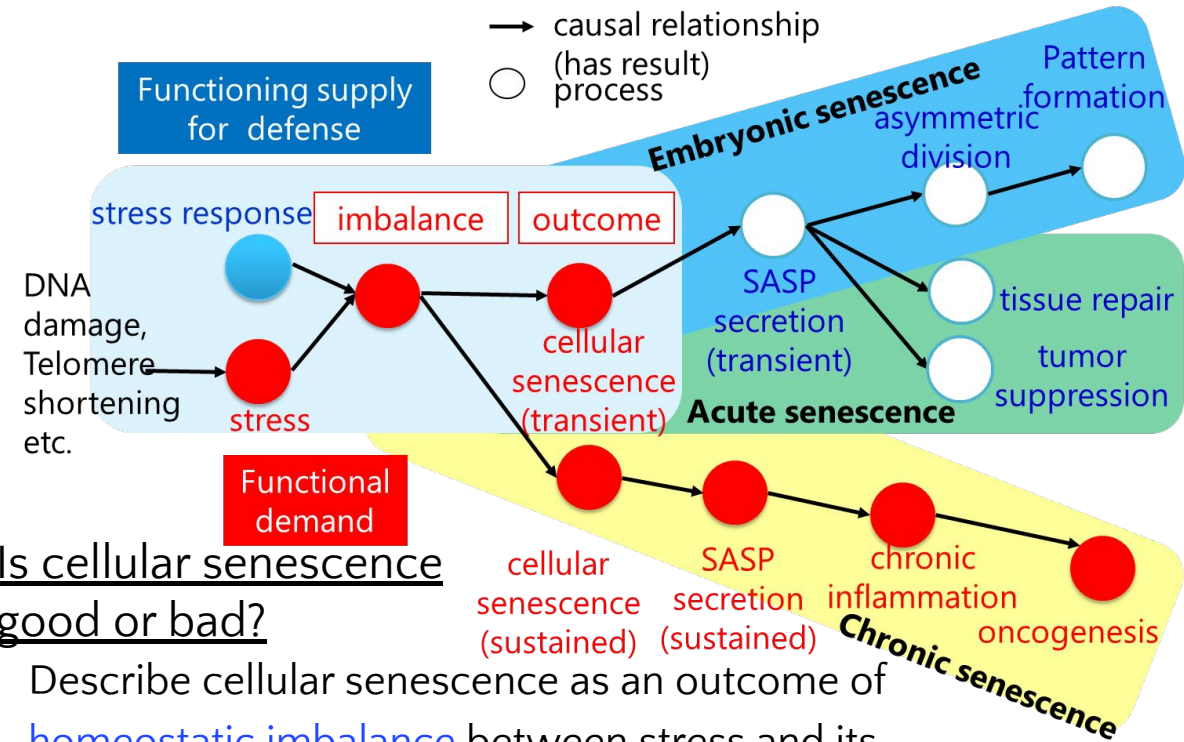
Causal relationships

Manual annotation from textbooks and review articles

Ontology editor: Protégé 5.5.0

Challenge: explicating the commonalities and differences from mixed-up knowledge

Homeostasis imbalance model



Is cellular senescence good or bad?

- Describe cellular senescence as an outcome of homeostatic imbalance between stress and its response
- Our imbalance model makes explicit the differences: Cellular senescence:
  - Benefits: tissue remodeling in embryonic and tumor suppression in acute senescent cells
  - Harmful effects: chronic inflammation, oncogenesis in chronic senescent cells

Challenge: Finding new mechanisms link to diseases

Why is cellular senescence a risk factor?

DL query:

Query (class expression)

'has result' some 'insulin resistance (very high) [chronic cellular senescence with type 2 diabetes]'

Execute Add to ontology

DL query: possible causes of insulin resistance

Query results

- Type B pancreatic cell exhaustion [chronic cellular senescence with type two diabetes]
- arrest of cell cycle G1/S phase transition (sustained) [chronic cellular senescence with type 2 diabetes]
- arrest of nuclear DNA replication (sustained) [chronic cellular senescence with type 2 diabetes]
- autophagy [chronic cellular senescence with type 2 diabetes]
- cell cycle arrest (sustained) [chronic cellular senescence with type 2 diabetes]

Explanation for: 'telomere shortening [chronic cellular senescence with type 2 diabetes] SubClassOf 'has result' some 'insulin resistance (very high) [chronic cellular senescence with type 2 diabetes]'

1) 'telomere shortening [chronic cellular senescence with type 2 diabetes] SubClassOf 'has result' some 'Type B pancreatic cell exhaustion [chronic cellular senescence with type two diabetes]'

Explanation 5

1) 'telomere shortening [chronic cellular senescence with type 2 diabetes] SubClassOf 'has result' some 'insulin resistance (very high) [chronic cellular senescence with type 2 diabetes]'

2) 'Type B pancreatic cell exhaustion [chronic cellular senescence with type two diabetes] SubClassOf 'has result' some 'hypofunction of insulin secretion [chronic cellular senescence with type 2 diabetes]'

3) 'hypofunction of insulin secretion [chronic cellular senescence with type 2 diabetes] SubClassOf 'has result' some 'hypofunction of mTORC2 signaling [chronic cellular senescence with type two diabetes]'

4) 'hypofunction of mTORC2 signaling [chronic cellular senescence with type 2 diabetes] SubClassOf 'has result' some 'AKT signaling [chronic cellular senescence with type two diabetes]'

5) 'AKT signaling [chronic cellular senescence with type two diabetes] SubClassOf 'has result' some 'FOXO3 signaling [chronic cellular senescence with type 2 diabetes]'

6) 'FOXO3 signaling [chronic cellular senescence with type 2 diabetes] SubClassOf 'has result' some 'positive regulation of autophagy [chronic cellular senescence with type 2 diabetes]'

7) 'positive regulation of autophagy [chronic cellular senescence with type 2 diabetes] SubClassOf 'has result' some 'autophagy [chronic cellular senescence with type 2 diabetes]'

8) 'autophagy [chronic cellular senescence with type 2 diabetes] SubClassOf 'has result' some 'positive regulation of senescence-associated secretory phenotype (SASP) secretion [chronic cellular senescence with type two diabetes]'

9) 'positive regulation of senescence-associated secretory phenotype (SASP) secretion [chronic cellular senescence with type two diabetes] SubClassOf 'has result' some 'senescence-associated secretory phenotype (SASP) secretion [chronic cellular senescence with type 2 diabetes]'

10) 'senescence-associated secretory phenotype (SASP) secretion [chronic cellular senescence with type 2 diabetes] SubClassOf 'has result' some 'insulin resistance (very high) [chronic cellular senescence with type 2 diabetes]'

Transitive: 'has result'

telomere shortening [chronic cellular senescence with type 2 diabetes]

Type B pancreatic cell exhaustion [chronic cellular senescence with type two diabetes]

positive regulation of senescence-associated secretory phenotype (SASP) secretion [chronic cellular senescence with type two diabetes]

senescence-associated secretory phenotype (SASP) secretion [chronic cellular senescence with type 2 diabetes]

insulin resistance [chronic cellular senescence with type 2 diabetes]

Inference using HoIP revealed 32 potential causes and various pathways associated with type 2 diabetes and chronic cellular senescence course, providing clues to unknown mechanisms.