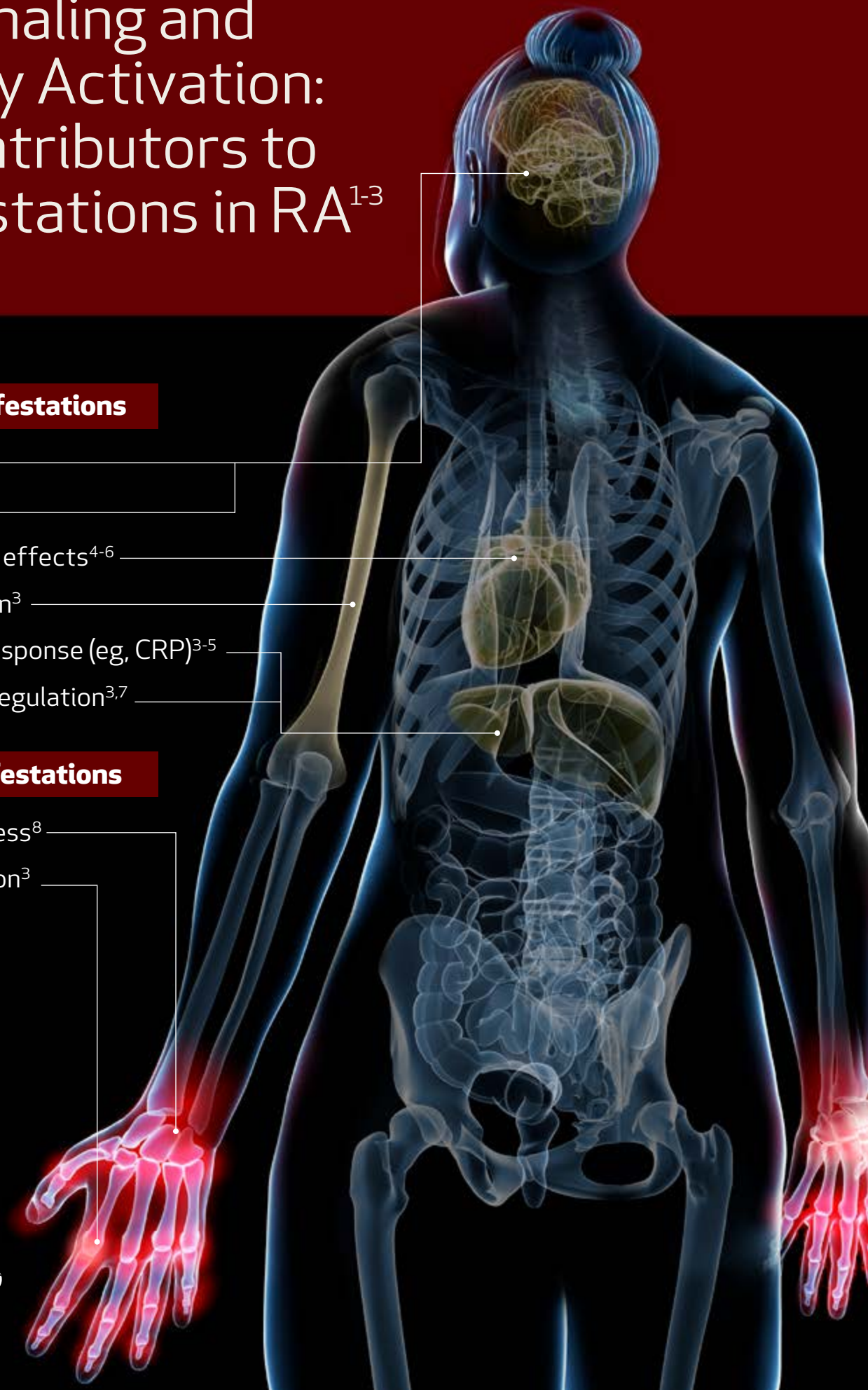
IL-6 Signaling and Pathway Activation: Key Contributors to Manifestations in RA[1-3]



Systemic manifestations

- Pain[2]
- Fatigue[2]
- Cardiovascular effects[4-6]
- Bone resorption[3]
- Acute-phase response (eg, CRP)[3-5]
- Metabolic dysregulation[3,7]

Articular manifestations

- Morning stiffness[8]
- Joint destruction[3]

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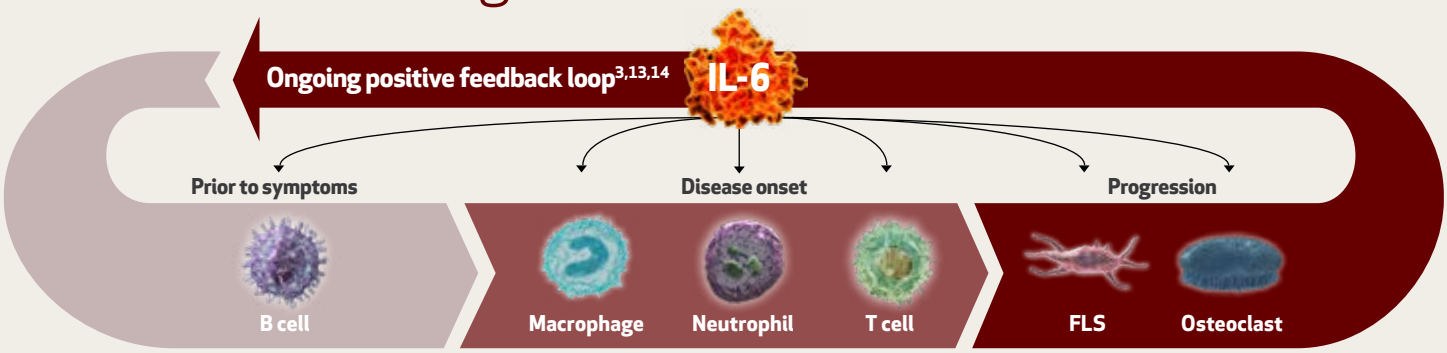
Serum levels of IL-6 can be up to 10x higher in patients with RA vs healthy controls[9,10]

- IL-6 levels are highest in the early morning—correlating with the peak of joint pain and stiffness[8,11,12]

Elevated IL-6 stimulates multiple cellular processes throughout the course of RA[3,13]



Stimulates **autoantibody production** by inducing B-cell differentiation[3]

Drives **chronic systemic inflammation** by acting on multiple cell types[3]

Induces **pannus formation** and **joint damage** by activating osteoclasts and FLSs[3,13,15]

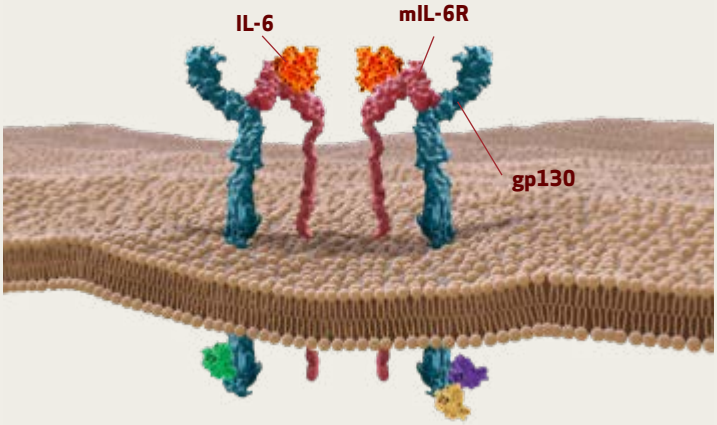
The unique dual-signaling mechanism of IL-6 allows for widespread biological effects[2,7,16-18]

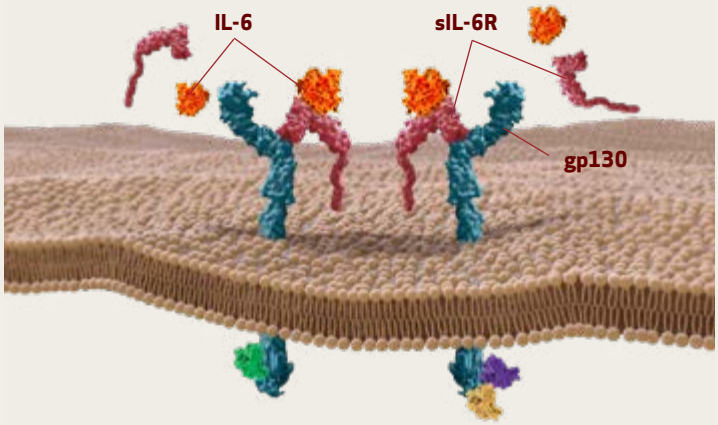
Cis-signaling[1,3,7,19]:

IL-6 binds with membrane-bound IL-6 receptors (mIL-6Rs)
Limited to cells expressing mIL-6R
(eg, hepatocytes and some leukocytes)

Trans-signaling[2,3,20]:

IL-6 binds with soluble IL-6 receptors (sIL-6Rs)
Enables interaction with all cells expressing gp130
(eg, osteoclasts, synoviocytes, neural cells)





The ubiquitous expression of gp130 allows IL-6 to act directly on almost all cell types[2,3,18]

IL-6 activates 3 distinct downstream signaling pathways—each with unique functions in RA[1,19,21-23]

- The interaction of IL-6 receptors with gp130 creates a functional signaling complex that then activates JAK proteins, initiating downstream signaling cascades[1,17,19]

MAPK[19]

Regulates the stability of proinflammatory cytokines

JAK/STAT[1,23]

Mediates gene expression and cell differentiation

JAK proteins primarily affect this pathway and potentially phosphorylate other kinases

PI3K[21,22]

Upregulates cell growth and survival and glucose metabolism

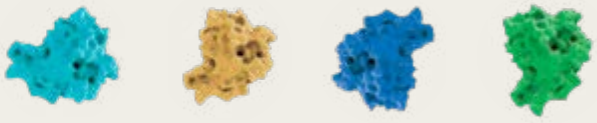
IL-6 and other mediators have distinct actions and effects in cell signaling and pathway activation[1,18,23-27]

Effects of IL-6 and JAK proteins

Proinflammatory functions

IL-6

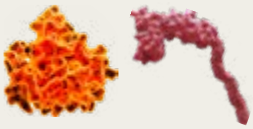
- IL-6 signals through its **specific receptor** (IL-6R), promoting proinflammatory functions[1,18]



Other physiological functions

- JAK proteins mediate signaling of **many receptors** involved in both proinflammatory functions and other physiological functions—and therefore can have nonspecific downstream effects[23,25]

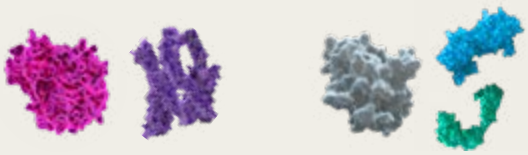
Effects of IL-6, TNF-α, and IL-1



Activates signaling

IL-6 **sIL-6R**

- The binding of IL-6 with its soluble receptor forms a **functional** complex that **activates** downstream proinflammatory signaling[1,24]



Inhibit signaling

- Both TNF-α and IL-1 form **nonfunctional** complexes with their soluble receptors that **inhibit** proinflammatory signaling[24,26,27]

Elevated IL-6 is a key driver of many systemic manifestations of RA that can impact patient quality of life[2,3,28]

Bone

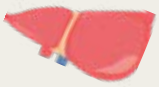
- Favors osteoclast over osteoblast function, promoting **bone resorption** that may manifest as **articular and systemic bone loss**[3,7]

CNS

- Mediates **pain** through action on the nociceptive system[2]
- Contributes to **fatigue** and affects **mood** by activating the HPA axis[2]
- Has been linked to **sleep disruption**[2,29,30]

Cardiovascular

- Contributes to **plaque development** and is associated with **atherogenesis** and **hypertension**[6,31-34]



Liver

- Increases expression of **CRP** and **hepcidin**, proteins that are key to the **acute-phase response**[3]

Adipose tissue

- Affects metabolism, thereby contributing to metabolic dysregulation that may manifest as **dyslipidemia** and **insulin sensitivity**[3-5]

Systemic manifestations of RA such as pain, fatigue, poor sleep, and effects on mood impact a significant proportion of patients with RA and are often ranked among their top concerns[2,35]

Abbreviations: CNS, central nervous system; CRP, C-reactive protein; FLS, fibroblast-like synoviocyte; gp130, glycoprotein 130; HPA, hypothalamic-pituitary-adrenal axis; IL-1, interleukin-1; IL-6, interleukin-6; IL-6R, IL-6 receptor; JAK, Janus kinase; MAPK, mitogen-activated protein kinase; mIL-6R, membrane-bound IL-6 receptor; PI3K, phosphoinositide-3 kinase; RA, rheumatoid arthritis; sIL-6R, soluble IL-6 receptor; STAT, signal transducer and activator of transcription; sTNFR, soluble tumor necrosis factor receptor; TNF-α, tumor necrosis factor α; TYK, tyrosine kinase.

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