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Review

류마티스 관절염에서 NLRP3 인플라마좀의 역할

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Role of NLRP3 Inflammasome in Rheumatoid Arthritis

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Objectives: Inflammasomes are molecular platforms that are generated inside cytoplasmic compartments. The objective is to mediate immunological responses of the host to cell damage and infection. Caspase-1 is triggered by inflammasome to generate interleukin-1β (IL-1β), an inflammatory cytokine, and pyroptosis, an inflammatory form of apoptosis.
Methods: In the past two decades, scientists have uncovered several inflammasomes. The most research has been conducted on NLRP3 inflamamsomes, whose activity can be stimulated by a variety of induction factors. However, the unregulated activation of NLRP3 inflammasomes is also a role in the etiology of several human disorders. Previous research has demonstrated that NLRP3 inflammasomes have a significant role in the innate and acquired immune systems, as well as in the prevalence of joint illnesses such rheumatoid arthritis.
Conclusion: Within the scope of this review, we will present a brief overview of the biological features of NLRP3 inflamamsomes as well as a description of the underlying mechanisms governing activation and regulation. In particular, we explore the function of inflammasomes in the development of rheumatoid arthritis as well as the promise of recently identified medicines that target inflamasomes.

Keywords : NLRP3, inflammasome, Rheumatoid arthritis, Treatment

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서 론

류마티스 관절염(RA)은 만성 염증 및 관절 통증을 특징으로 하는 자가면역 질환으로[1], 활액관절의 염증, 연골 파괴, 뼈 침식, 관절주위 탈석회화로 설명될 수 있으며, 결국 관절 기능 장애를 초래한다[2]. RA는 세계에서 가장 흔한 염증성 자가면역 질환 중 하나로써[3], 전 세계적으로 1990년에 비해 연간 발생률이 8.2% 증가하여[4,5], 세계 인구의 1-2%가 RA를 앓고 있다[6].

류마티스 관절염의 증상으로 볼 때 한의학에서 는 이를 痺症과 歷節風의 범주에 포함시킬 수 있는데 痺症은 肢體, 關節의 疼痛, 酸楚, 麻木, 重着, 活動障碍 등의 증상을 보이며[7,8], 歷節風은 관절이 붓고 심한 疼痛을 호소하며 관절이 屈伸不利하는 것을 특징으로 하는 병으로 紅腫, 下肢腫痛, 脚腫如脫, 手指變曲, 夜間痛甚 등의 증상이 나타난다[7,8]. 이에 과거부터 牛膝과 같은 한약제나 利濕活通湯과 같은 한약복합제제의 치료효과가 국내에서 꾸준히 보고되어 왔다[8].

대상 및 방법

1. 연구동향

자가면역은 RA의 발병기전의 첫 번째 단계이며, 항시트룰린화 펩티드 항체(ACPAs)와 같은 높은 혈청 농도의 자가항체는 RA의 특징이지만, 일부 환자들에서 혈청음성이다[1,9]. 이와 같이 RA의 정확한 발병기전은 불분명하지만 유전학, 흡연, 비만, 감염, 치주 질환, 심지어 장내 미생물총까지 RA의 발병과 관련이 있는 것으로 현재 생각되고 있다[10,11].

2. 류마티스&염증복합체

2-1 유전적 요소

유전적 요소는 질병 유발에 기여하는 여러 유전자와 함께 RA 병인에서 중추적인 역할을 한다[2,4]. RA 발달과 관련된 유전적 변이의 대부분은 면역 반응과 관련된 유전자 내에 있으며, 인간 백혈구 항원(HLA) 변이와 염증복합체의 유전적 변이가 주요한 유전적 위험 인자이다[4]. NLRP1 유전자의 변이는 NLRP1의 발현을 증가시켜 류마티스 관절염과 더불어 일부 염증성 질환 제1형 진성 당뇨병[1,12]과 백반증 및 관련 자가면역 질환[13]의 발병에 위험 요소로 작용한다[14]. NLRP3 유전자의 돌연변이는 여러 질병에서 필수적인 역할을 한다는 것이 이전에 보고되었으며[15-18], PBMCs에서 NLRP3 염증복합체 관련 유전자 NLRP3, ASC 및 caspase-1의 발현이 RA 병인 및 질환 활성과 관련될 수 있고 중요한 역할을 할 수 있음이 나타났다[3].

2-2. 염증

RA의 연골 분해는 과도한 면역 반응으로 인해 발생한다[19]. IL-1, TNF, IL-6 및 IL-17을 포함한 전염증성 사이토카인은 기질 메탈로프로테이나제(MMP) 및 아그레카나제 예: ADAMTS-4 및 ADAMTS-5)와 같은 연골 분해 효소의 생성을 유도하며 활액 섬유아세포에서 연골세포에 의한 세포외 기질 생성을 억제한다[20,21]. 이러한 염증반응은 주로 염증복합체를 형성함으로써 발생한다. 염증복합체는 복합체 내에 결합하여 존재하는 비활성형 pro-caspase-1을 가수분해하여 caspase-1으로 활성화시키고, 그 결과 활성화된 caspase-1에 의해 IL-1β 및 IL-18와 같은 염증복합체 특이적 사이토카인을 대식세포에서 생성, 분비하며, 동시에 대식세포의 괴사인 파이롭토시스(pyroptosis)를 유발한다[22-25]. RA의 활막 및 활액에 풍부한 TNF, IL-6 및 IL-1과 같은 전염증성 사이토카인은 활막 섬유아세포에 의한 RANKL 발현을 촉진하여, TNF 계열 사이토카인 및 대식세포 집락 자극 인자(M-CSF)와 함

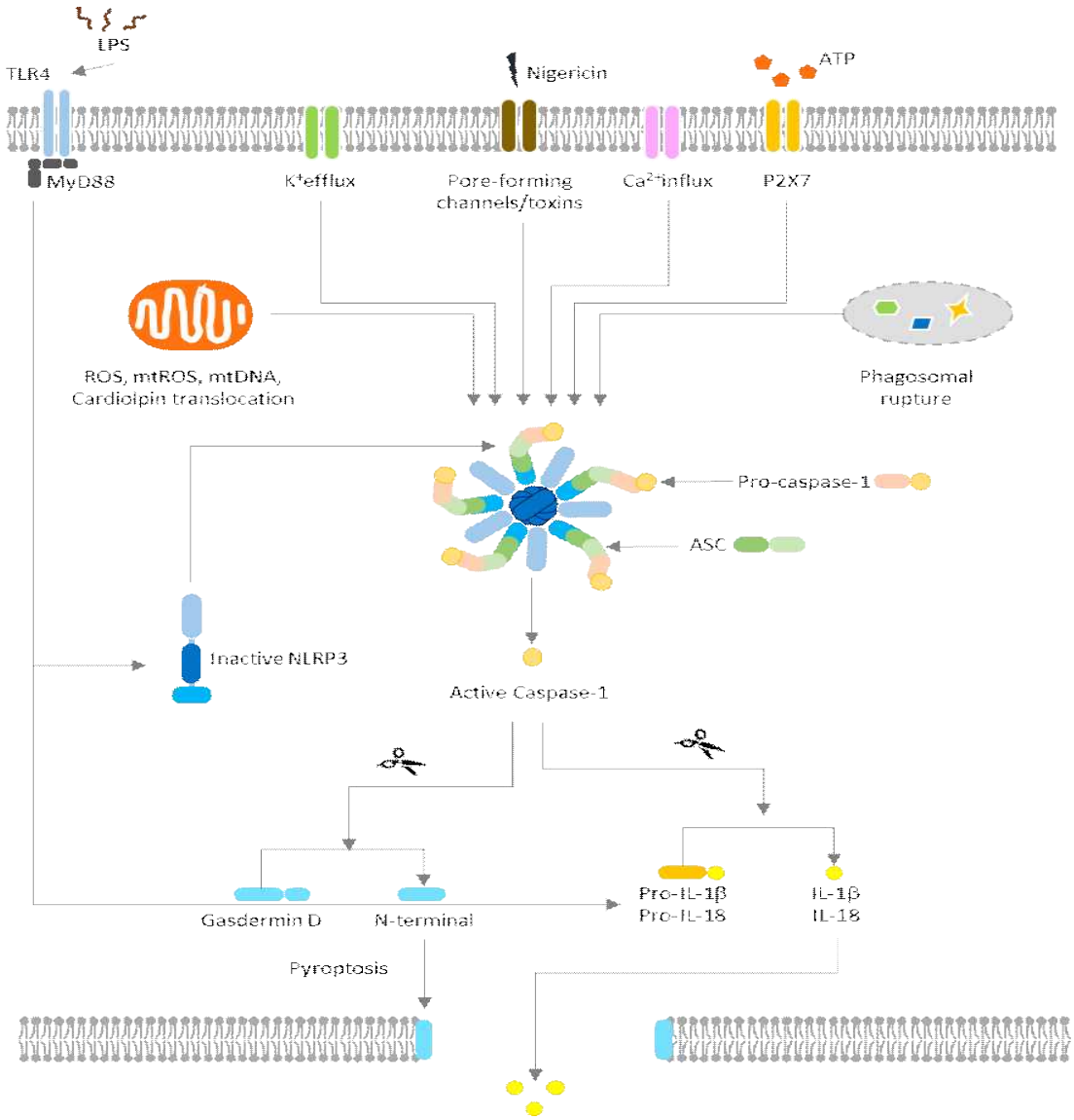

Figure 1. The main NLRP3 inflammasomes. The canonical NLRP3 inflammasome needs a priming signal, also called Signal 1, which is often sent by toll-like receptors (TLRs) and turns on NF-&B, which makes NLRP3 proteins. PAMPs or DAMPs send an activating signal, which is also called Signal 2. PAMPs and DAMPs cause changes in the cell's physiology. These changes show up as ion efflux and influx, mitochondrial dysfunction, or the phagosome bursting. These changes in physiology are picked up by NLRP3, which tells the kinase NEK7, ASC, and caspase-1 to put together the NLRP3 inflammasome.

께 파골세포를 생성한다[26-28]. 또한 인터루킨(IL)-1ϐ, IL-6, IL-18 및 종양 괴사 인자(TNF)는 Th17 세포 분화를 촉진하며 연골 성분의 합성을 감소시키며[29], 여러 기전을 통해 조골세포 생성을 억제한다[27].

2-3 NLRP1

NLRP1 염증복합체는 NLR 패밀리 중 가장 먼저 규명된 NLRP1과, ASC 그리고 procaspase-1로 이루어진 단백질 복합체이며[22),23)], 이는 pro-interleukin-1β(pro-IL-1β), pro-IL-18 및 pro-IL-33을 절단하여 활성 사이토카인 IL-1β, IL-18 및 IL-33을 방출한다[30)]. IL-33은 또한 인간 RA 활막에서 높게 발현되는 것으로 밝혀졌으며, IL-33의 혈청 수준은 류마티스 인자 및 항시트룰린화 단백질 항체를 포함한 IgM 및 RA 관련 자가항체의 생성과 상관관계가 있다[31)].

2-4 NLRP3

NLRP3은 말초 혈액 백혈구에서 우세하게 발현되며[32),33)], 염증 자극에 반응 시, 단백질(ASC) 및 caspase-1 프로테아제와 결합된 NLRP3 염증복합체를 (Figure 1) 빠르게 형성한다34). NLRP3 염증복합체의 형성은 caspase-1을 활성화시키고35), 이는 전염증성 사이토카인 IL-1β 및 IL-18의 성숙을 (Figure 1) 초래한다[36)]. IL-1β는 면역 반응에서 다기능적 역할을 하여 사이토카인 생성을 유도하고 T 세포 활성화 및 항원 인식을 향상시키며 타고난 면역 세포를 감염 부위로 안내하며[37),38)], NF-κB 신호전달 캐스케이드의 활성화를 유도하여 사이토카인, 케모카인 및 다양한 전염증 매개체를 코딩하는 유전자의 전사 활성화를 초래한다[39),40)]. 이러한 NLRP3 염증복합체의 과활성화는 과도한 염증을 초래하고 결과적으로 불필요한 숙주 조직 손상을 초래하여[41)], RA 질환의 유지에 기여한다[42)].

결 론

다수의 연구들은 또한 NLRP3가 RA에서 상향조절된다는 것을 입증하여 NLRP3 염증복합체가 RA 병인에 필수적인 역할을 할 수 있음을 추가로 시사하였으며[42-46)], 또한, NLRP3이 RA를 포함하는 자가면역 질환에서 유망한 치료 표적이 될 수 있다는 것이 제안되었다.

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The authors declare no conflict of interest.

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