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Experimental animal models of chronic inflammation

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ABSTRACT

Inflammation is a general term for a wide variety of both physiological and pathophysiological processes in the body which primarily prevents the body from diseases and helps to remove dead tissues. It has a crucial part in the body immune system. Tissue damage can recruit inflammatory cells and cytokines and induce inflammation. Inflammation can be classified as acute, sub-acute, and chronic. If it remained unresolved and lasted for prolonged periods, it would be considered as chronic inflammation (CI), which consequently exacerbates tissue damage in different organs. CI is the main pathophysiological cause of many disorders such as obesity, diabetes, arthritis, myocardial infarction, and cancer. Thus, it is critical to investigate different mechanisms involved in CI to understand its processes and to find proper anti-inflammatory therapeutic approaches for it. Animal models are one of the most useful tools for study about different diseases and mechanisms in the body, and are important in pharmacological studies to find proper treatments. In this study, we discussed the various experimental animal models that have been used to recreate CI which can help us to enhance the understanding of CI mechanisms in human and contribute to the development of potent new therapies.

1. Introduction

Inflammation is a crucial part of the body immune system. It is defined by 5 features: pain, heat, redness, swelling, and loss of function (Punchard et al., 2004). Tissue damage for any reason such as chemical agents, pathogens, and trauma can recruit inflammatory cells and cytokines and induce inflammation (Pahwa et al., 2020). The inflammation process helps the body to debride necrotic and damaged tissues and clean the body from pathogens (D'Arcy, 2019). Based on how long it takes for the inflammation to be resolved, it is divided into 3 groups: 1- **acute inflammation** which starts rapidly and symptoms last for a few days. 2- **sub-acute inflammation** which lasts for 2–6 weeks. 3- **chronic inflammation (CI)** which lasts a prolonged period of time and even can remain lifelong (Fig. 1) (Zhang et al., 2019a; Michels da Silva et al., 2019; Šoltés and Kogan, 2010). Inflammation starts by activation of special receptors such as damage associated molecular pattern (DAMP) sensing receptors or pattern recognition receptors (PRRs) due to the entrance of antigen or tissue damage in the body (Franklin et al., 2018). These receptors trigger other inflammatory pathways such as NF-κB which increases cellular resistance to pathogens and causes immune cells recruitment and the production of pro-inflammatory cytokines (Medzhitov, 2008). If the antigen is eliminated successfully, inflammation would be resolved in the few days as the lipid mediators switch from pro-inflammatory cytokines to anti-inflammatory cytokines such as lipoxin (Serhan and Savill, 2005). Usually, an inflammation caused by a physical damage is resolved spontaneously but sometimes it can be prolonged and stay in the body. In this situation, damages to the tissues precipitated and in the context of this inflammation, various diseases such as cardiovascular diseases (CVD), diabetes, arthritis, autoimmune diseases, cancer, and several other diseases can occur. Thus, CI has a crucial role in development and progression of various disorders (Chen et al., 2018; Cruz and Kang, 2018). Obesity increases inflammatory cytokines and also the production of leptin, a potent inflammatory cytokine, is increased in obese people (Tilinca et al., 2018). The possible mechanism for this phenomenon is the activation of NF-κB. The NF-κB pathway is involved in different cellular metabolisms such as pro-inflammatory cytokine production (Jiang et al., 2018; Khajebishak et al., 2019). Smoking and some toxic gases lead to the cellular damage but persistent exposure to these agents induces CI in the lung and further chronic obstructive pulmonary disease (COPD) which is the third leading cause of death worldwide. CI can exacerbate lung damage and leads to disease progression by 1- increase in pro-inflammatory cytokine

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production 2- induction of ROS production 3- activation of leukocytes in the lung (Lee et al., 2009). The immune system and induced inflammation also help the body to defend against cancer development (Shoham et al., 1980). On the other hand, several studies have shown that CI has roles in the development, progression and metastasis of cancer (Multhoff et al., 2012). Thus, cancer cells induce inflammation in their micro-environment by attracting different parts of the immune system like mast cells and macrophages (Shihab et al., 2020). These cells produce different substances which help tumoral cells to be spread more easily, for example, vascular endothelial growth factor (VEGF) (Min et al., 2021; Hwang et al., 2020). VEGF is an angiogenic factor and is produced by macrophages (Min et al., 2021). ROS and pro-inflammatory cytokines which are produced in the tumor microenvironment increase NF-κB expression. NF-κB increases cell survival, production of pro-inflammatory cytokines, metastasis, and cancer progression (Gaptulbarova et al., 2020; Zinatizadeh et al., 2021). Additionally, cancer cells produce immune system inhibitor cytokines such as IL-10 that can suppress cytotoxic T-cells (Batchu et al., 2021). Additionally, inflammation has a critical role in the development and progression of Alzheimer's disease (AD). Overproduction of tau and amyloid β (Aβ) act as antigen within the CNS and activates microglia, recruits other immune cells such as lymphocytes, and triggers inflammatory pathways such as NF-κB (Pluta and Ułamek-Kozioł, 2019; Gerrits et al., 2021; Eiser and Fulop, 2020). These changes lead to the neuronal degeneration and exacerbation of AD. The main pathophysiological mechanisms of irreversible damages of autoimmune diseases such as rheumatoid arthritis, lupus, and multiple sclerosis is CI as these diseases induce a hyper-inflammation state in the body (Chen et al., 2019). Taken all together, inflammation plays a key role in the development of various diseases and understanding its mechanisms helps us to find effective therapeutic approaches. Animal models are valuable tools for understanding inflammation mechanisms. Herein, we aim to review the literature on seven main animal models of CI. Based on our literature search, we have chosen the most common animal models that are used for induction of CI.

2. Animal models of CI

Animal studies are one of the essential bases of various disciplines, and their use in science has a long history. The most important aspect of animal models is ethics. Researchers could not induce disorders in human for their studies even if the intended disease is curable. It is completely unethical and could lead to the irreversible physical and psychological damages. Thus, researchers used animal models for different purposes, such as induction of diseases and finding therapeutic targets. This extensive use is because of the genetic similarities between human and some animal species, especially mammals (Poznyak et al., 2020). However, working with animals has certain rules that should be followed to minimize the suffer and anxiety of used animals. Several guidelines have been developed for this purpose including preparing proper facilities to provide enough food and water, care, and physical health; using recent technologies and predictive models instead of animal models, reducing the number of animals used in the study, and minimizing the pain and distress caused to animals (Pasupuleti et al., 2016; LUHalsey and Bury, 2017). Based on the previous writings of the Greeks in the 2nd and 4th centuries, the early animal studies on living animals were probably performed by Aristotle and Erasistratus (Dey et al., 2010). The role of animal studies in the progression of science, especially medicine, is impossible to refuse. Animals that are chosen to be used in experiments to induce specific symptoms or diseases should have certain criteria. First, they should have a similar phenotype to the human. Second, processes leading to diseases should be identical between humans and those animals. Third, the animals should be sensitive to the pharmacological or non-pharmacological interventions applied to treat that disease in human (Nestler and Hyman, 2010). Recent studies have updated the criteria and have added some other features such as the similarity between biological mechanisms, and their affordable cost (Poznyak et al., 2020; Belzung and Lemoine, 2011).

As it was mentioned above, CI is considered as an essential part of various diseases such as atherosclerosis, diabetes mellitus (DM), renal failure, obesity, cancer, and heart failure (Fig. 2) (Geovanini and Libby, 2018; Stienstra et al., 2007; Rodríguez-Hernández et al., 2013; Garcia et al., 2010; Peppa et al., 2004; Shirazi et al., 2017; Ballerini et al., 2022). Thus, understanding the mechanisms of this phenomenon helps researchers to develop new therapeutic approaches. One of the primary tools for understanding the pathogenesis of CI is using animal models and studying its mechanisms, related disorders, and methods of control. Induction of CI in animals not only helps scientists to understand the cellular and intracellular pathways involved in but also helps them to find better treatments. However, there is a variety of methods for animal model induction and each of them has some advantages and disadvantages. Common animal that is used for CI studies is mouse. In addition to

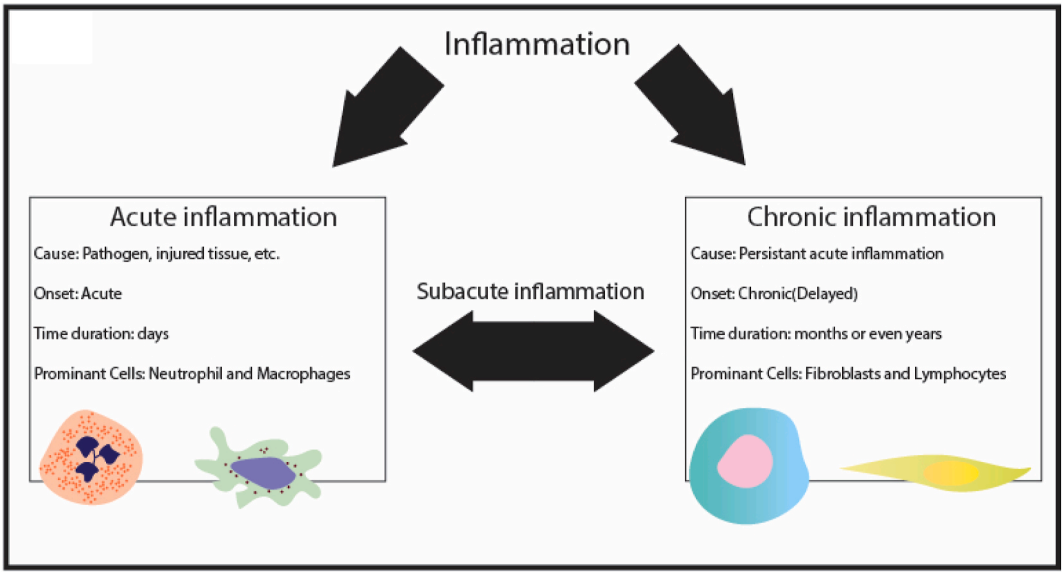

Fig. 1. A comparison between Acute, subacute, and chronic inflammation. Notice that Subacute inflammation is a state between acute and chronic inflammation and has some features of acute and chronic inflammation.

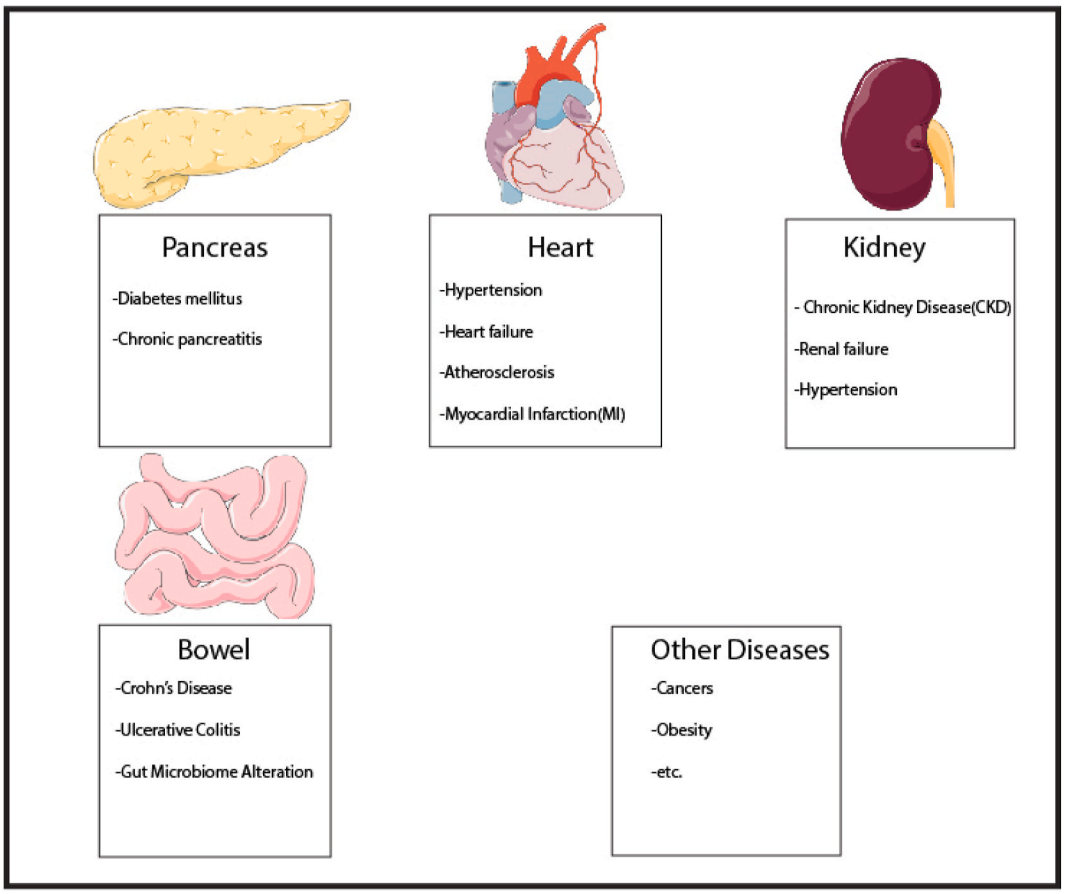

Fig. 2. CI causes several diseases due to its related damages. Parts of the figure were drawn by using pictures from Servier Medical Art. Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/).

the similar response to infectious diseases, many similar processes such as aging and high similarity between mouse and human genome(about 97.5%) have made these animals ideal for animal studies (Dawson, 2011; Bryda, 2013; Bogaards et al., 2000). C57BL/6 and Balb/c are two common strains that have been used in experimental studies. These mice have some properties that make them more efficient for establishing CI models. They have differences in their immune responses which make each of them suitable for certain inflammatory diseases. C57BL/6 mice have strong Th1 immune response and IFN-γ production, high activity of complement system, and can induce immune tolerance easily. Balb/c mice have strong Th2 immune response, a common response in allergic reactions and infectious diseases, high production of IgG1 and IgA, high complement activity, and low interferon production. Additionally, Balb/c mice produce stronger humoral response against antigens in comparison with C57BL/6 strain (Bleul et al., 2021; Aoki et al., 2019; Zhang et al., 2023; Laurenti et al., 2004; Kuroda et al., 2002; Koo and Gan, 2006; Watanabe et al., 2004).

In this review, we discussed the different methods for the establishment of CI animal models (Table 1);

2.1. Lipopolysaccharide (LPS)

LPS is one of the known agents for the induction of CI. It is used in a variety of studies that have investigated physiology, immunology, and metabolism (Rathinam et al., 2019; Yirmiya et al., 2001). As this agent is related to septicemia, it can also be used in the studies that assess the role of antibodies and inhibitors in targeting LPS (Baumgartner et al., 1990; Jang et al., 2017).

2.1.1. LPS structure and function

LPS (also called "endotoxin") is a molecule composed of lipids, polysaccharides, and O-antigen. This molecule is a major part of the outer membrane of gram-negative bacteria and is involved in their pathogenicity (Alexander and Rietschel, 2001). lipid A, the core oligosaccharide, and the O antigen are the main parts of LPS and O antigen is the most variable part and its composition varies from strain to strain. It incites a strong immune response which makes it favorable for immunological studies (Freudenberg et al., 2008). The persistent presence of LPS in the blood can cause CI (Hamada et al., 1990). Some studies suggested that the CI in obesity is due to gut microbiome dysregulation which increases gram-negative proliferation and LPS production (Saad et al., 2016). Toll-like receptor 4 (TLR-4) belongs to the pattern recognition receptor (PRR) family. PRRs are important in the innate immune system and TLR-4 is one of the first receptors that has been found that is able to recognize the LPS. Activation of TLR-4 by LPS leads to an increase in NF-κB expression (Vaure and Liu, 2014). As mentioned above, this pathway leads to the production of pro-inflammatory cytokines and as a result, induces inflammation.

2.1.2. Methods of induction of CI by LPS

In Table 1, studies that used LPS as a trigger of CI are mentioned. Most of these studies used this agent to assess its effect on neurodegeneration and the mechanisms of CI in obesity and diet. Different methods are used to deliver LPS to the animal body such as IP injection, adding it to the drinking water, and releasing continuously by implanting minipump or slow-release pellets in the animal. Ostos MA and colleagues used LPS for induction of atherosclerosis in Male C57bl/6 Apo E deficient mice. At the 10th week of their birth, they were randomly divided into three groups (n = 4 per group). LPS (50 μg) was

Table 1
Different methods to induce CI in animal models.

Method	Author	Title	Dose and injection	Model	Main cellular changes	Main inflammatory cytokines	Reference
LPS	Ostos MA et al.	Implication of natural killer T cells in atherosclerosis development during a LPS-induced CI	- 50μg, once a week for 10 weeks - 50 μg, single Both IP	Mice C57bl/6, Male, Apo E deficient (in vivo)	T lymphocytes subsets including: $CD4^+ = 35.2\%$ $CD8^+ = 23\%$ NK1.1 = 5.7%	IFN-y, and TNF-α	Ostos et al. (2002)
	Droke EA et al.	Soy isoflavones avert CI-induced bone loss and vascular disease	0, 0.133, 1.33, 13.3 μg/day for 30 days Slow-release pellets	Mice C57bl/6, female (in vivo)	Decrease of lymphocytes dose dependently: from 90.4 in placebo to 65.7 in high dose group Increase of neutrophils dose dependently: from 4.5 in placebo to 12 in high dose group	TNF-α	Droke et al. (2007)
	Qin L et al.	Systemic LPS Causes Chronic Neuroinflammation and Progressive Neurodegeneration	5 mg/Kg single dose IP	Mice C57bl/6,	Increased microglia	TNF-α, MCP-1, IL-1b, and NF-κB p65	Qin et al. (2007)
	Liang W et al.	Metabolically induced liver inflammation leads to NASH and differs from LPS- or IL-1b-induced chronic					
inflammation	5 μg/day for 6 weeks Minipump	APOE3L.CETP mice	4 fold increase in mononuclear and neutrophils of liver	–	Liang et al. (2014)		
	Mine Y et al.	Chinese Sweet Leaf Tea (Rubus suavissimus) Mitigates LPS-Induced Low-Grade CI and Reduces the Risk of Metabolic Disorders in a C57BL/6 Mouse Model	300 μg/Kg for 15 weeks (from week 5 to week 20) Through drinking water	C57BL/6 mice	Increased macrophage infiltration in white adipose tissue from 0.55 to 2.52	TNF-α, IL-6, MCP-1 and adiponectin	Zhang et al. (2019b)
	Cuenca N et al.	Systemic inflammation induced by lipopolysaccharide aggravates inherited retinal dystrophy	60 μg/Kg for 40 days(P20 to P60) IP	P23H rat	12% increase in Iba1+/MHC-II− cells and 35% increase in Iba1+/MHC-II + cells and about 30% increase in CD11b+, $CD45^+$ cells	IL-1α, IL-1β, CXCL3	Noailles et al. (2018)
	Mine Y et al.	Lactobacillus pentosus S-PT84 prevents LPS-induced low-grade chronic inflammation in a C57BL/6J mouse model	300 μg/Kg for 15 weeks (from week 5 to week20) With drinking water	C57BL/6 mice	About 20% increase of adipocytes with infiltrated macrophages	TNF-α, MCP-1	Zeng et al. (2019)
OVA	Bonfield et al.	Human mesenchymal stem cells suppress chronic airway inflammation in the murine ovalbumin asthma model	- 100 μl of 10 μg of ovalbumin emulsified in 1.5 mg of Al(OH)3 IP - 1% wt/vol ovalbumin (Serhan and Savill, 2005; Watanabe et al., 2004) in PBS in day 14 for 4 weeks Intranasal	Balb/c Mice	Lymphocytes and eosinophils were increased and macrophages were decreased	IL-5, IL-13, IFN-y, MIP-1α	Bonfield et al. (2010)
	Consden et al.	Production of a chronic arthritis with ovalbumin. Its retention in the rabbit knee joint	- ovalbumin in 0 9 per cent with saline, 20 mg/ml which emulsified in an equal volume of Freund's incomplete adjuvant, 0.2 ml at 5 regions repeated 3 weeks later Intradermally	Rabbits of the old english strain	–	–	Consden et al. (1971)
	Yamagata et al.	Interleukin-18-deficient mice exhibit diminished chronic inflammation and airway remodeling in ovalbumin-induced asthma model	OVA (1% wt/vol diluted in PBS) repeated twice each week for 12 weeks. Aerosolized - 50 μg of OVA absorbed to 100 μg of Alum in 200 μl of PBS on days 0 and 14. IP - 50 μg of OVA absorbed to 100 μg of Alum in 200 μl of PBS on days 0 and 14. IP OVA (1% wt/	Specific pathogen-free (SPF) C57BL/6-wild type (IL-$18^{+/+}$) mice and C57BL/6 IL-18-deficient (IL-$18^{-/-}$) mice	Increased number of eosinophils, neutrophils, and lymphocytes	IL-5, IL-12, IFN-y	Yamagata et al. (2008)

(*continued on next page*)

Table 1 (*continued*)

Method	Author	Title	Dose and injection	Model	Main cellular changes	Main inflammatory cytokines	Reference
			vol diluted in PBS) repeated twice each week for 12 weeks. Aerosolized				
	Xiao et al.	Glucagon Like Peptide-1 (GLP-1) Modulates OVA-Induced Airway Inflammation and Mucus Secretion Involving a Protein Kinase A (PKA)-Dependent Nuclear Factor-κB (NF-κB) Signaling Pathway in Mice	10 μg of OVA in 100 μg of Al $(OH)_3$ on day 0, 7 and 14. IP - From day 15–81, the mice were challenged with 5% OVA for 1.5 h once daily. Aerosolized	BALB/c mice	Increased number of neutrophils, macrophages, eosinophils, and lymphocytes	TNF-α, IL-5	Zhu et al. (2015)
	Liu et al.	MicroRNA-221 modulates airway remodeling via the PI3K/AKT pathway in OVA-induced chronic murine asthma	5% OVA in saline from week 3 to week 10 through respiratory tract Aerosolized	BALB/c mice	About 35% increase of eosinophils	IL-6, TNF-α	Pan et al. (2020)
	Du et al.	Administration of Pigment Epithelium-Derived Factor Inhibits Airway Inflammation and Remodeling in Chronic OVA-Induced Mice via VEGF Suppression	- 100 μg of OVA emulsified in 100 μL of aluminum hydroxide gel. - On day 21 airway challenged with 1% OVA for 8 weeks Aerosolized	BALB/c mice	About 55% increase of eosinophils	IL-5	Zha et al. (2016)
Cotton pellet(CP)	Sultana et al.	Anti-inflammatory effect of ethanolic extract of carica papaya leaves and indomethacin in cotton pellet induced granuloma in animal model	one sterile cotton pellet weighing 30 mg each was implanted subcutaneously in one groin region of each rat	Long Ewan Norwegian rat	–	–	Sultana et al. (2019)
	Saidi et al.	Preliminary Evaluation of the Acute and Sub-Acute Anti-Inflammatory Activities of Aqueous and Butanol Leaf Fractions of Olax subscorpioidea Oliv. (Olacaceae)	a sterile CP(50 mg) soaked in 0.2 ml distilled water, 0.13 mg streptomycin and 0.1 mg penicillin was implanted subcutaneously in groin region	Wistar rat	–	–	Saidi et al. (2020)
CLP	Singer et al.	Cecal ligation and puncture results in long-term central nervous system myeloid inflammation	–	C57BL/6 mice	About 10% increase of neutrophils and monocytes	CXCL1, CX3CL1, CXCL10, TNF-α, CCL2, CCL7, CCL10	Singer et al. (2016)
	Osuchowski et al.	Sepsis chronically in MARS: systemic cytokine responses are always mixed regardless of the outcome, magnitude, or phase of sepsis	–	ICR mice	–	–	Osuchowski et al. (2012)
	Zaghloul et al.	Forebrain cholinergic dysfunction and systemic and brain inflammation in murine sepsis survivors.	–	BALB/c mice	Increased macrophages and astrocytes	TNF-α, IL-1β, IL-6, CXCL1	Zaghloul et al. (2017)
TiO2 NP	Park et al.	Induction of CI in mice treated with titanium dioxide nanoparticles by intratracheal instillation	5, 20 or 50 mg/kg Intratracheal instillation, delivered with a 24-G catheter	ICR mice	Increased macrophages	IL-1β, IL-2, IL-9	Park et al. (2009)
	Jia et al.	Effect of Long-Term Intake of Dietary Titanium Dioxide Nanoparticles on Intestine Inflammation in Mice	Diet with 0.1% TiO2 NP10, NP50, or NP100	C57BL/6 mice	About 10%, 1.5%, 2.5% decrease of T $CD4^+$, Tregs, and macrophages respectively.	–	Shi et al. (2013)
	Chen et al.	Titanium dioxide nanoparticles induce emphysema-like lung injury in mice	0.1 mg per mouse (low dose) or 0.5 mg per mouse (high dose) in a 50 μl aliquot Intratracheal instillation	ICR mice	Increased macrophages	CXCL5, MCP-1	Chen et al. (2006)
	Boland et al.	Impact of serum as a dispersion agent for in vitro and in vivo toxicological assessments of TiO_2nanoparticles	2.56 mg/ml in ultrapure water with or without 2% (w/v) mouse serum Intratracheal instillation	C57BL/6N mice	Increased neutrophils and lymphocytes	IL-8	Vranic et al. (2017)
	Cristobal	Vascular toxicity of ultra-small TiO_2 nanoparticles and single walled carbon nanotubes *in vitro* and in vivo	- 1-cell stage embryos exposed to NPs in the water (10–1000 mg/l) - 1-cell stage embryos exposed to NPs via injection of them to yolk sac	Transgenic Tg (fli1a: $EGFP)^{y1}$zebrafish	–	–	Bayat et al. (2015)

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Table 1 (*continued*)

Method	Author	Title	Dose and injection	Model	Main cellular changes	Main inflammatory cytokines	Reference
P.gingivalis	Bartold et al.	Effect of Porphyromonas gingivalis-induced inflammation on the development of rheumatoid arthritis	About 10^{11} bacteria impregnated in polyurethane sulfate was implanted on the rats' back	DA rat	Increased lymphocytes and macrophages	–	Bartold et al. (2010)
	Velsko et al.	Active invasion of oral and aortic tissues by Porphyromonas gingivalis in mice causally links periodontitis and atherosclerosis	10^9 bacteria inoculated orally for four consecutive days per week every third week for four (12 week) or eight (24 week) weeks	ApoE null B6.129P2-Apoe^{tm1Unc}/J mice	About 5% increase of macrophages	Ccl5, IL1β, IL-3, IL5	Velsko et al. (2014)
	Gallimidi et al.	Periodontal pathogens*Porphyromonas gingivalis* and *Fusobacterium nucleatum*promote tumor progression in an oral-specific chemical carcinogenesis model	300 μl of 10^{10}bacteria/ml with 2% carboxymethylcellulose (CMC) orally	BALB/c mice	–	IL-6	Binder Gallimidi et al. (2015)
CFA	Shirani et al.	Comparative evaluation of the protective effects of oral administration of auraptene and umbelliprenin against CFA-induced chronic inflammation with polyarthritis in rats	single subcutaneous injection of 0.1 ml CFA (heat killed Mycobacterium tuberculosis in paraffin oil, 0.5 mg/ml)	Wistar rats	–	TNF-α, IFN-y, IL-2, IL-17	Shirani et al. (2021)
	Vinayak et al.	Quercetin Ameliorates CFA-Induced Chronic Infammatory Hyperalgesia via Modulation of ROS-Mediated ERK1/2 Signaling and Inhibition of Spinal Glial Activation In Vivo	100 μl CFA in the right hind paw Intraplantar injection	Charles Foster strain rats	–	TNF-α	Kumar and Vinayak (2020)
	DeLeo et al.	Complete Freunds adjuvant-induced peripheral inflammation evokes glial activation and proinflammatory cytokine expression in the CNS	CFA suspended in an oil / saline (1 : 1) emulsion intraplantar injection into the surface of the left hind paw	Sprague–Dawley rat	Increased microglial activation	TNF-α, IL-1β, IL-6	Raghavendra et al. (2004)
	Sperlágh et al.	Contribution of platelet P2Y12 receptors to chronic Complete Freund's adjuvant -induced inflammatory pain	15 μL CFA in saline Intraplantar injection	C57BL/6 and (P2ry12 −/−) mice	–	IL-1α, IL-1β, IL-6, TNF-α	Bekő et al. (2017)
	Coelho et al.	Thiamine and riboflavin inhibit production of cytokines and increase the anti-inflammatory activity of a corticosteroid in a chronic model of inflammation induced by complete Freund's adjuvant	Injection of CFA into the paw plantar surface and the tail base(0.1 ml for each site), second injection on day 2(0.1 ml for each site)	Holtzman rats	–	TNF-α, IL-6	Menezes et al. (2017)

injected intraperitoneally once every week for 10 weeks in the LPS group. Mice of the second group were injected with LPS only once (LPS1 group) and the last group was injected with a phosphate-buffered saline (PBS) with a similar dose of LPS once every week for 10 weeks (PBS group). For analyzing the basal immunological response in wild-type C57Bl/6 animals, they used two groups (n = 5 per group). They injected LPS and PBS into these groups respectively. They showed that LPS increased the atherosclerotic plaque size and plasma autoantibody titer against oxidized low-density lipoprotein. Taken all together, their result confirmed that LPS can Induce CI which can lead to atherosclerotic plaque formation in Apo E deficient mice (Ostos et al., 2002). Induction of atherosclerosis, specifically in ApoE deficient mice, via LPS injection suggested that hypercholesterolemia which is a property of apoE0 mice have a role in immunological modulation (Ostos et al., 2002; Snapper et al., 1999). Furthermore in consistent with other similar studies, these mice showed a greater level of anti-oxLDL antibodies with an involvement of Th1 and Th2 in production of antibodies due to the higher titr of IgG2a and IgG1 produced by these cells, respectively; which also found in patients with coronary artery disease (Snapper et al., 1999; Ehara et al., 2001).

Droke EA et al. used LPS for the induction of CI that leads to bone loss and vascular disease. They wanted to study the effects of soy isoflavone on the reduction of bone loss and vascular diseases. Eight-week-old intact female C57BL/6 mice were used in this study. Lipopolysaccharide (E. coli Serotype 0127: B8) was added to slow-release pellets which were used to provide a consistent dose of LPS for 30 days. After anesthetizing, the pellets were implanted in the dorsal region of the necks of the animals subcutaneously. This study was composed of two phases. In phase one, they used 4 doses of LPS 0, 0.133, 1.33, and 13.33 μg LPS/d. These doses were selected based on prior studies (Smith et al., 2006). In phase two, the effect of soy isoflavones (IF), a type of polyphenol found in legumes such as soybean, was studied. Their results showed that LPS administration resulted in the decrease of trabecular bone volume and number. Additionally, trabecular bone strength and stiffness were also compromised in response to LPS which are the signs of CI in the bone. Taken all together, this study demonstrated that using the slow release

pellets of LPS could be a useful technique for the induction of CI as it did not change the animal behavior (Droke et al., 2007). Chronic inflammation and upregulation of TNF-α increase osteoclast differentiation and activity which increases bone resorption (Balga et al., 2006). Additioanally, induction of apoptosis in osteoblasts and the reduction of osteoblast progenitor cell recruitment are other aspects of chronic inflammation in the bones (Armour et al., 2001; Dumitrescu et al., 2004).

Qin and his colleagues injected LPS to produce chronic neuroinflammation and progressive neurodegeneration in C57bl/6 mice. Two main groups were concluded in this study. 1- A group in which the TNF receptor was knocked out (TNFR1/R2$^{-/-}$). 2- The control group (TNFR1/R2$^{+/+}$). The former group were lacking both the p55 and p75 TNF receptors. Male C57BL/6, TNFR1/R2$^{-/-}$, and TNFR1/R2$^{+/+}$ mice were intraperitoneally injected with a single dose of LPS, TNF-α, and 0.9% saline (as a control group). Their result showed that systemic injection of LPS could activate microglia and pro-inflammatory cytokine expression such as TNFα, MCP-1, and IL-1β (Qin et al., 2007). Production of TNF-α as an indirect effect of LPS injection leads to the microglial activation in the brain. LPS has a poor passage through blood-brain-barrier (BBB) and its effects are through production of cytokines in periphery, entry of these molecules to the brain, and further induction of neuroinflammation (Nadeau and Rivest, 1999; Crews et al., 2006).

Liang et al. used 5 μg LPS for the induction of CI in the liver of mice. ApoE*3-Leiden mice were crossed with hemizygous human CETP transgenic mice and the presence of the human ApoE3 protein and human CETP protein in the plasma was confirmed by ELISA in offspring. One group's diet did not change and remained on chow (control group). The other animals received an HFD (24% (w/w) for 10 weeks and at the end of the 10th week, they were matched into the groups based on total plasma cholesterol, triglycerides, and body weight. HFD feeding was continued in all groups. Until week 16, groups were treated with one of the following treatments: LPS from Salmonella minnesota by minipump at 5 mg per day; recombinant murine IL-1b by minipump at 100 ng per day; dietary Carbohydrate; dietary cholesterol (1% (w/w) mixed into HFD). Mice anesthetized by isoflurane and osmotic minipumps were placed subcutaneously in the back region. Two control groups treated with either HFD + PBS (minipump) or HFD only were used in this study. Their results confirmed that LPS can induce CI (Liang et al., 2014). NF-κB is the main pathway for induction of NASH in the liver. However, it could not induce NASH *per se* and other inflammatory pathways would be required. The main cellular changes of NASH in the liver is neutrophil infiltration and the recruitment of these cells within the liver not only needs non-metabolic (classical) inflammatory chronic triggers (IL-1b, LPS) but also metabolic inflammatory triggers (high carbohydrate, cholesterol) (Liang et al., 2014; Orlichenko et al., 2010).

2.2. Ovalbumin (OVA)

Another potent CI inducer is OVA. Numerous studies have used this agent to induce CI in the respiratory system to study asthma.

2.2.1. OVA structure and function

OVA is the major protein that is present in the egg white. It is a globular protein and Its molecular weight is 43 kDa and is composed of 385 amino acids (Strixner et al., 2011). After synthesis in the cell, this protein is affected by several post translational modifications such as N-terminal acetylation, phosphorylation, and glycosylation (Nisbet et al., 1981). Interestingly, this protein has an internal signal sequence instead of an N-terminal signal sequence found in most of secreted proteins. Additionally, this signal sequence would be preserved in the protein structure after maturation (Robinson et al., 1986). Environmental factors can impact on the shape and the structure of this protein, especially the denaturation can leads to its aggregation (Abd El-Salam et al., 2016). OVA can induce allergic reaction which makes it suitable for immunological and allergy studies (Caubet and Wang, 2011). The access to large quantities of this protein makes it a good target for general studies of protein structures and properties (Ma et al., 2020). Since the OVA has 3 dimensional homology to serpin family proteins but unlike them does not have serine protease inhibitor activity, it can be used for studies about serpin. This feature can help scientists to compare the structure of OVA with serpin and identify the crucial parts of serpin for inhibitory activity (Moss et al., 2021). Additionally, OVA is used for proteomics studies and it is considered a proper marker of molecular weight for electrophoresis gel calibration (Saba et al., 2001).

2.2.2. Induction of CI by OVA

There are several studies that have considered OVA as a proper factor that can induce CI in animal models. OVA can increase the sensitivity and reactions of airways and further increase inflammatory cells such as eosinophils, OVA-specifc IL-4 and IL-5 cytokines, and airway hyperresponsiveness. These mechanism can induce the symptoms of asthma (Lee et al., 2010). Bonfield et al., used OVA as an asthma trigger in BALB/c mice. They wanted to assess the effect of human mesenchymal stem cells (hMSC) on Asthma. BALB/c mice were sensitized by intraperitoneal injections (100 μl) of 10 μg of OVA emulsified in 1.5 mg of Al (OH)3. After that, mice were exposed to 1% wt/vol OVA (Serhan and Savill, 2005; Watanabe et al., 2004) in PBS by intranasal challenge every day for 4 weeks from day 14. In the sham group sensitization and challenges were done by sterile PBS. During the 4th week of the challenge (the last week of experiment) mice were given 1×10^6 hMSCs and harvested after 7 days. Their results showed that OVA is a potent factor for the induction of CI which was followed by asthma in mice (Bonfield et al., 2010). In another study, Yamagata S et al. assessed the role of IL-18 in the chronic airway inflammation and airway remodeling. They used two animal models: 1- normal C57bl/6 and 2- IL-18 deficient mice. This study was composed of four groups: 1- the PBS-sensitized and exposed group 2- the PBS-sensitized and OVA-exposed group 3- the OVA-sensitized and PBS-exposed group 4- the OVA-sensitized and -exposed group. In the second group the amount of OVA used for exposure was 1% wt/vol diluted in PBS. The mice were exposed for 20 min twice every day and for 12 weeks. In the third group sensitization with OVA was done by injection of 50 μg of OVA dissolved in 100 μg of Alum and 200 μg PBS on the 0th and 14th day. The fourth group used the same dose as the second and third groups for exposure and sensitization respectively. Interleukin content of Bronchoalveolar lavage fluid of these groups confirmed chronic airway inflammation. Their result showed that OVA could successfully induce neutrophil recruitment in the airways of healthy IL-18$^{+/+}$ mice. Additionally, OVA induced peribronchial fibrosis, increased smooth muscle thickness, and mucus expression in lung tissues of both IL-18$^{+/+}$ and IL-18$^{-/-}$ mice. These results confirmed that OVA could induce CI and consequently asthma in mice (Yamagata et al., 2008).

In 1971, Consden. R et al. used OVA for the induction of chronic arthritis in the knee joint of an old English strain bred rabbit. Their method was different as they want to assess the CI in the knee joint. Firstly, they dissolved OVA in 0.9 percent Saline (20 mg/ml). Then, they emulsified this solution with an equal amount of Freund's incomplete adjuvant (FIA) and 2 mg dead dried human tubercle bacilli. They injected 1 ml of this emulsion intradermally into the intrascapular region. This injection was repeated after 3 weeks. It was suggested that in normal rabbits, OVA was eliminated rapidly but rabbits that were immunized by OVA showed much greater retention of this molecule in their knee joints. Their study showed for the first time that the utilization of the OVA for the induction of CI in the knee joint is successful (Consden et al., 1971). OVA in the joints acts as foreing antigen, recruits inflammatory cells, and triggers further cytokine production and inflammation in the joints.

Accordingly, OVA can be considered a stimulant for inflammation. Thus, it can be used in experiments that aim to study CI in animal models.

2.3. Cotton pellet (CP)

One of the common methods for CI induction is the implantation of a cotton pellet in the animal model and producing inflammation, subacutely and chronically which makes it favorable for immunological studies.

2.3.1. Structure and function

Cotton wool is cut into pieces to form cotton pellets. The cotton is a soft fiber and grows in bolls. Cotton plant or *Gossypium* is a genus of flowering plants from the mallow family. The fiber is made of cellulose but a minor percentage of fat, pectin or, water can also incorporate into its structure (Li et al., 2016; Haigler et al., 2012; Sun et al., 2007). Elongation of the single-celled extension of the seed epidermis leads to cotton fiber formation (Haigler et al., 2012).

2.3.2. Methods for induction of CI by CP

Sultana and colleagues assessed the anti-inflammatory effect of ethanolic extract of *Carica papaya* leaves and indomethacin. Their experiment was carried out on 48 Long Evan Norwegian rats. For the induction of granuloma, one sterile cotton pellet weighing 30 mg each was implanted subcutaneously in one groin region of each rat. The animals were divided into four groups. They treated as follows: Group 1 received normal saline orally daily for 14 days (control group). Group 2 received ethanolic extract of *Carica papaya* leaves at a dose of 50 mg/kg body weight daily for 14 days. Group III received ethanolic extract of *Carica papaya* leaves at a dose of 100 mg/kg body weight orally daily for 14 days. Group IV received indomethacin at a dose of 5 mg/kg body weight orally daily for 14 days. Their results confirmed the role of CPs in the induction of granuloma and CI (Sultana et al., 2019).

Saidi et al. evaluated the anti-inflammatory effect of *Olax subscorpioidea* Oliv. To induce inflammation, they used CPs in male Wistar rats. A sterile CP (50 mg) soaked in 0.2 ml distilled water, 0.13 mg streptomycin, and 0.1 mg penicillin were implanted subcutaneously in the groin region. For nine days after the implantation of cotton pellet, distilled water (1 ml/kg), aqueous or butanol fraction (1,000 mg/kg), or ASA (300 mg/kg) was administered orally. On day 10, the cotton pellet was dissected out, weighed, and dried at 60 °C until the weight remained constant. The difference in the weight of the cotton pellet before and after implantation was recorded and considered as a granuloma tissue deposit. Their results confirmed that CP implantation leads to granuloma tissue formation and CI (Saidi et al., 2020). CPs are usually used for the induction of granuloma which occurs in the setting of CI. When inflammation is prolonged, the macrophages and lymphocytes can be combined and consequently form granuloma. Based on this matter that the inflammation can be produced as a response against CP, we can use this material in animal experiments for further investigation of the CI and also study about the proliferative phase of chronic inflammation, as CP acts as an antigen and trigger immune system for production of immune response.

2.4. Cecal ligation and puncture (CLP) and CI

One of the methods that is developed for induction of CI in animals is CLP. Despite previous methods that are described above, this method, as its name implies, is done by doing surgery on the animal model instead of specific substance administration. The common method used for CLP is summarized; First, the abdominal wall should be realex by local administration of lidocaine and then the animal should be sedated. Under the sterile condition, 1–2 cm laparotomy is performed, the cecum is ligated with silk suture completely and punctured with a 19-gauge needle. Finally, incisions are closed by surgical clips. Singer BH et al. used CLP to induce sepsis and studied about the effect of sepsis on long term neuroinflammation. The method that was used for CLP was same as what is mentioned above. This study was done on male C57BL/6 mice and had three groups 1- CLP 2- sham 3-unoperated. They showed that CLP can result in chronic CNS inflammation (Singer et al., 2016). Osuchowski. M and colleagues used CLP for the induction of sepsis in ICR mice. They used the common method for CLP as mentioned above. The aim of this study was the identification of the inflammation and signaling pathways involved in it in chronic sepsis. (Osuchowski et al., 2012).

Usually, CLP is used as a proper model to study sepsis. It is because the colonization of the bacteria in the cecum after the ligation leads to inflammation and swelling of the cecum. Finally, the cecum is ruptured and its content spreads in the abdominal space which results in peritonitis, sepsis, and death. However, some studies have used this model for other long term inflammations.

2.5. Titanium dioxide nanoparticle (TiO2 NP) and CI

Titanium is the ninth most abundant element on the earth. It cannot be found in metallic form in nature due to its great affinity to oxygen and other elements (Shi et al., 2013). Titanium dioxide nanoparticles are used widely in industry because of their high catalytic activity and in different products such as sunscreens according to their ability to ultraviolet blocking. Traditionally, these nanoparticles were used as negative control in many studies because of their low solubility and low toxicity. But this opinion was challenged by Lee and their colleagues. They suggested that the long inhalation of TiO2 NPs (TNP) leads to lung tumor development in rats (Lee et al., 1985). Further researches have shown that these particles can cause CI and inflammatory-related diseases (Shi et al., 2013). Park. K et al. used Tio2 NPs for the induction of CI in mice. They wanted to show the pathways involved in the induction of CI by Tio2 NPs. Initially, they suspended TNP in PBS and confirmed that it was a uniform suspension by ultrasonic wave. Then, TNP was delivered to the mice by intratracheal instillation with a 24 G catheter. There were four study groups in this study: 1- control group, 2- a group of mice received 5 mg/kg TNP, 3- a group of mice received 20 mg/kg TNP, and 4- a group of mice received 50 mg/kg TNP. Their result revealed that TNP could induce CI in the mice lung via the T helper-2 mediated pathway (Park et al., 2009). Jia. X and colleagues delivered TNPs to the C57BL/6 mice to study about the effect of Tio2 on gut inflammation. Mice in this study received a normal diet or diet with 0.1% TNP. The TNPs had 3 different sizes: 10, 50, and 100 nm. First, mice were housed in specific pathogen-free facilities. After that the study was done on two groups: 1- normal mice 2- germ free mice which received ciprofloxacin and metronidazole. Both groups (normal and germ-free mice) were divided into four subgroups: 1- control, 2- TNP10-received mice, 3- TNP50-received mice, and 4- TNP100-received mice. Their result showed that in normal mice TNP could lead to weight loss and intestinal inflammation but this effect was not observed in pathogen-free mice which suggests that the effect of Tio2 is mediated by the intestinal microbiome (Mu et al., 2019).

Taken all together, these studies have confirmed the potential role of Tio2 NPs in the induction of CI as Tio2 NPs could induce ROS production and damage to the different tissues. Additionally, macrophages which engulf these particles produce IL-1β, TNF-α, and IL-6 and further activate T cells which could be differentiated to T helpers($CD4^+$) or T cytotoxic ($CD8^+$). Both of them induce autoimmune response and exacerbate inflammation of tissues (Park et al., 2009).

2.6. Complete Freund's adjuvant (CFA)

One of the methods for induction of CI, especially in the joints, is using Complete Freund's Adjuvant (CFA). This agent has wide usage in animal studies of CI specifically in the joints to induce chronic arthritis.

2.6.1. CFA ingredients and function

CFA is composed of desiccated mycobacterium, paraffin oil, and mannide monooleate (Hanlon et al., 2010). This substance is used commonly for the induction of arthritis and CI in the joints called

adjuvant-induced arthritis (AA). Several studies showed that mycobacterium can activate toll-like receptors (TLRs) and increase IL-12 production in dendritic cells (DCs) (Kelly et al., 2004). Both TLRs and IL-12 are involved in inflammation (van der Putten et al., 2019). Additionally, early inflammatory cytokine and chemokine release after the injection of CFA is another aspect of inflammation caused by CFA. But the exact mechanism of the contribution of mycobacterium and paraffin oil needs further studies to be elucidated (van den Berg et al., 2015).

2.6.2. CFA and CI induction

One of the common application of CFA is for the induction of CI with polyarthritis. Shirani and colleagues used CFA for the induction of CI with polyarthritis for the investigation of two coumarin derivates. Eighty adult male Wistar rats were used in this study. In experiment groups, single subcutaneous injection of 0.1 ml CFA consisted of 0.5 mg/ml heat killed Mycobacterium tuberculosis in paraffin oil into the left hind footpad was administered. Single subcutaneous injection of PBS was administered in the left hind paw of the vehicle control group with no inflammation-inducing agent. Their result confirmed that CFA can be used for the induction of CI with polyarthritis (Shirani et al., 2021).

Induction of chronic inflammatory hyperalgesia is another use of CFA. Kumar et al., investigated the effect of Quercetin on the CFA-induced chronic inflammatory hyperalgesia in rats. The experiment was composed of 6 groups. The first group received an intraplantar (i.pl.) injection of 100 μl normal saline (NS). Others were injected with 100 μl CFA (i.pl.) in the right hind paw. Their study confirmed the role of CFA in chronic inflammatory hyperalgesia (Kumar and Vinayak, 2020).

Recent studies have used CFA not only for the induction of arthritis but also for other CI variations such as chronic neuroinflammation and pain studies. Taken all together, probably CFA can be used for induction of CI in a variety of organs but its exact mechanism for induction of pain and hyperalgesia along with inflammation has not introduced well.

2.7. Porphyromonas gingivalis

Entering bacterium into the body can induce immunological reactions and inflammation which makes them favorable for immunological studies. However, some bacteria such as tuberculosis activate the immune system slightly or do not activate it at all. Also, the immune system has a tolerance against some of the bacteria such as gut microbiome. Accordingly, a bacteria that is proper for activating immunological reactions and producing inflammation as the result, can play a role in inducing CI in animal models. It has been reported that porphyromonas gingivalis can be used as a trigger for CI induction in animal experiments.

2.7.1. Porphyromonas gingivalis structure and function

P.gingivalis is a non-motile gram negative bacterium belonging to the Bacteroidetes phylum. It is an anaerobic, rod-shaped, and pathogenic bacterium that makes black colonies in blood agar. This bacterium has several virulence factors which help it to induce immune activation and also damage the host more effectively. One of these virulence factors is gingipain. P.gingivalis produces Arg-gingipain and Lys-gingipain which are endopeptidases and have pivotal roles in the metabolism of this bacterium. These enzymes can cleave pro-inflammatory cytokines such as IL-8, IL-1β, IL-2, IL-6, and TNF-α. Elevated levels of C-reactive protein and IL-6 have been seen in patients with periodontal diseases (Cavrini et al., 2005). Additionally, they can evade the immune system by the inhibition of IL-2 accumulation within the T helper-2. P.gingivalis induces local inflammation in the oral cavity which can lead to gingival ulceration and local vascular changes. These changes have the potential to increase the incidence and severity of bacteremia (D'Aiuto et al., 2004). Discussing all of the roles of these enzymes is out of the scope of this article, so we just have mentioned some studies which used this organism to induce CI.

2.7.2. P.gingivalis and CI

Most of the studies have tried to elucidate the association of P.gingivalis and poor oral hygiene with other diseases such as atherosclerosis and other CI-induced diseases. Bartold et al., in a study aimed to evaluate the effect of P.gingivalis on the development of rheumatoid arthritis. This study was done based on the studies which had reported the probable correlation between the chronic extra-synovial inflammatory lesions and the induction and severity of experimental arthritis (Bozkurt et al., 2006; Mercado et al., 2000; Lagervall et al., 2003). They induced CI lesions by the use of polyurethane sponges impregnated with heat-killed Porphyromonas gingivalis into the backs of rats. Then, after 35 days, they induced adjuvant arthritis by injection of the mycobacterium cell wall in CFA. After 21 days, the histological assessments of the implanted sponges confirmed the establishment of CI lesions. This study showed that P.gingivalis could be used for the induction of CI lesions and for the investigating the effects of pre-existing inflammation in the body on the development of diseases such as rheumatoid arthritis (Bartold et al., 2010). P. gingivalis by induction of chronic inflammation in the joints lead to the immune system dysregulation and removes the restraint from the immune system which further associated with autoimmune diseases such as rheumatoid arthritis. These results are also consistent with clinical findings that patients with periodontitis have severe rheumatoid arthritis and vice versa (Bartold et al., 2010).

Another study that used P.gingivalis for the induction of CI is the study of Velsko and colleagues. Velsko et al., investigated the role of chronic P.gingivalis infection and periodontal diseases on the development and progression of atherosclerotic plaque. The cultured P. gingivalis inoculated orally to induce oral infection at a dose of 10^9 in reduced transport fluid (RTF) −4% carboxymethylcellulose (CMC). Sham group received RTF-4% CMC only. Their results confirmed that P. gingivalis is potent to cause periodontal inflammation which could exacerbate atherosclerotic plaque progression (Velsko et al., 2014). P. gingivalis disrupt NO production, a vasodilator agent, directly infect aortic tissue, and also change *Fga, Fgb* and *Serpinb2* genes expression which are important in atheroma formation (Velsko et al., 2014; Tousoulis et al., 2012; Vasquez et al., 2012).

Collectively, these studies confirm that P.gingivalis can be used as a proper periodontal CI model.

3. Conclusion

Animal models are inseparable components of experimental studies. In this review, we summarized different methods for the induction of CI in animals. Some of these methods are used for induction of systemic CI and some are used for inducing localized CI. Further studies would be needed to confirm the usage of these substances as potent CI inducers. The investigation of CI helps us to understand the inflammatory mechanisms and have better insights into the chronic inflammatory diseases as they are some of the most challenging diseases due to their significant costs and are hard to treat and be controlled. Besides, it helps us to find better therapeutic targets which leads to more favorable results, as most of the current therapeutic agents developed for these chronic diseases, are helpful in just controling or reducing of the progression of these diseases and are not capable to completely cure them. Thus, CI studies help scientists to design better drugs and provide better treatments with lesser complications for patients.

CRediT authorship contribution statement

Mahdi Rafiyan: Investigation, Writing – original draft. **Shaghayegh Sadeghmousavi:** Writing – review & editing. **Milad Akbarzadeh:** Conceptualization. **Nima Rezaei:** Validation, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial

interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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