

ناج اندر
بیم جان افزا
حکایتی که
میسازد

Autoimmunity and smoking

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Cigarette smoking, nicotine, the harms

- Exposure of cigarette smoke was reported to induce **autophagy and inflammation in experimental animals and humans**.
- **The toxicity mechanism of cigarette** smoke on immune system in organisms has **not been entirely investigated**
- On the other hand, there are some data on **immunomodulatory effect of nicotine**
- There are some studies about the effect of **smoking on the important autoimmune diseases including: Lupus, Rheumatoid Arthritis, Inflammatory Bowel Disease, Multiple Sclerosis, Behcet's Disease and...**

Three cigarettes are shown on the left side of the slide, with their lit tips pointing towards the right. The cigarettes are white with orange filters and are arranged diagonally.


The inflammatory pathway

- Exposure to cigarette smoke reduced the viability of cells in a dose-dependent manner
- Cigarette smoke was shown to **augment the production of numerous pro-inflammatory cytokines** such as TNF- α , IL-1, IL-6 and to **decrease the levels of anti-inflammatory cytokines** such as IL-10.
- Tobacco smoke via multiple mechanisms leads to **elevated IgE** concentrations and to the subsequent development of **atopic diseases and asthma**.
- Some of **the inhibitory effects of nicotine** have been attributed to its effect on **the $\alpha 7$ nicotinic acetylcholine receptor** found in macrophages, T-cells and B cells.
- Activation of this receptor has been shown to reduce production of the pro-inflammatory cytokines TNF- α , IL-1 β and IL-6, suppressing Th1 and Th17 reactions, but not Th2 reaction




The effects of smoking on the immune system

- While it is better evident how cigarette smoke evokes airway diseases more mechanisms are being revealed linking this social hazard to autoimmune disorders, for instance:
- Via the production of antibodies recognizing citrullinated proteins in **rheumatoid arthritis** or by the elevation of anti-dsDNA titers in **systemic lupus erythematosus**
- The burning of tobacco at the tip of the cigarette heats the air drawn through it.
- The heated air then passes through unburned tobacco causing nicotine and other components to evaporate. As the air later cools, some of these components condense into smoke



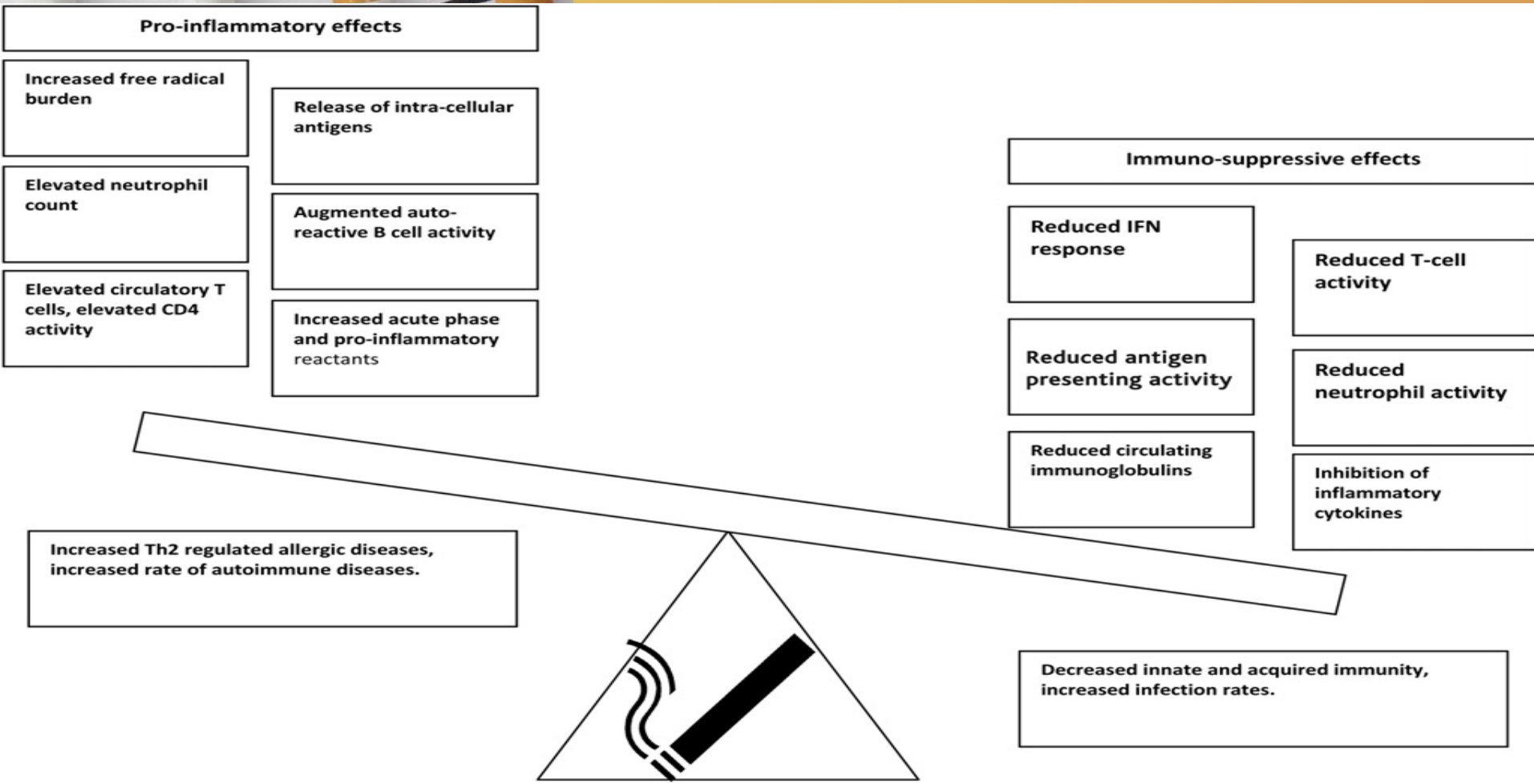
The effects of smoking on the immune system

- The smoker inhales the nicotine-enriched aerosol, with particle size in the micron range, permitting efficient alveolar deposition and rapid absorption in the systemic blood. Burning cigarettes produce as much as 6000 different components including polycyclic aromatic hydrocarbons, tobacco glycoprotein and some metals, many of which are known to be antigenic, cytotoxic, mutagenic, or carcinogenic, and most of them are generated by the burning tobacco.
- Chronic exposure of rats to the vapor phase of cigarette smoke does not lead to significant changes in the immune response, indicating that immunosuppressive properties of cigarette smoke are mainly associated with the particulate phase of cigarette smoke.



The effects of smoking on the immune system

- Studies show that maternal smoking alters both the adaptive and innate immune arms of newborns
- Smoking is associated with both release and inhibition of proinflammatory and anti-inflammatory mediators. A large network of pulmonary and systemic cytokines is involved in chronic inflammation of smokers.
- The inhibitory effects of cigarette smoking have been attributed to nicotine, hydroquinone (the phenolic compound in cigarette tar) and to carbon monoxide in the smoke. Nicotine had suppressive effect on IL-6 inflammatory cytokine levels.
- It can inhibit IL-10 production. That effect is utilized for treatment with nicotine patches in patients with inflammatory bowel disease
- IL-8 is a potent leukocyte chemotactic factor, specific for neutrophils. In studies performed in





- Endotoxin (lipopolysaccharides, LPS) is one of the **most potent inflammatory agents known**. Tobacco smoke increases endotoxin exposure by far, more than hundred times compared with nonsmoking environment.
- These high levels could contribute to an **elevated IgE and the subsequent development of atopic diseases and asthma**. CD14 is the receptor for LPS and other bacterial wall derived components. There is an interaction between asthma severity and levels of CD14 and IgE.
- Maternal smoking in pregnancy resulted in a diminished innate production of antigen-presenting cell (APC) cytokines, as well as an impaired response to TLR ligands.
- Smokers had (IgA, IgG, and IgM) up to 10-20% lower than those of non-smokers.



Smoking and RA

- The only well established risk factor is cigarette smoking.
- Tobacco exposure also increases the risk of RA in women.
- The risk of RA was significantly elevated with 10 pack-years or more of smoking and increased linearly with increasing pack-years.
- Importantly, the risk of RA remained substantially elevated until 10-20 years after smoking ceased.
- A meta-analysis reviewing this association indicated that the risk for smokers of developing RA is about twice that of nonsmokers.
- RA patients with a history of smoking were found to show a poor response to treatment with TNF antagonists and Methotrexate. Response failure was associated with the intensity of previous smoking, irrespective of smoking status at initiation of anti-TNF therapy.



Smoking and SLE

- Cigarette smoking has been **proposed to be a trigger for both development and severity of SLE** and many studies have examined that correlation with mixed results
- smoking has a mild, yet significant contribution, **elevating the risk for developing SLE** with an OR of 1.50
- Current smokers have been reported to have more **serious cutaneous and neuropsychiatric involvement than former or never-smokers**
- Several studies have demonstrated a decreased response **to anti-malarial therapy in patients suffering from cutaneous lupus erythematosus**
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Smoking and vasculitis syndromes

- **Thromboangiitis obliterans (Buerger's disease):** a vasculitis in young, mostly male smokers that affects the small and medium-sized arteries and veins of the limbs. **Discontinuation of smoking is the only proven definitive therapy.**
- Hypersensitivity to type I and III collagen associated with the presence of anti-collagen or anti-elastin antibodies has been suggested. **These abnormalities are considered to be non-specific and the pathological process underlying the disease is still unknown.**



- **Behçet's disease (BD):** Smokers have been reported to exhibit oral aphthae less frequently than non-smokers, and during periods of smoking, patients with BD had fewer oral aphthae (both in number and frequency) compared to periods of abstinence. The overall presence of aphtous stomatitis has also been observed to be higher in non-smokers than in smokers. These effects are thought to result from the inhibitory effect of nicotine exposure on IL-8, and to some extent IL-6.
- **Goodpasture's syndrome:** is an autoimmune condition characterized by glomerulonephritis and hemoptysis. The clinical presentation is correlated to the presence of anti glomerular basement membrane (anti-GBM). Pulmonary hemorrhage is closely correlated to smoking regardless of absolute anti-GBM titers



Smoking and inflammatory bowel disease

- The effect of smoking on UC seems to only postpone the event, as the RR for UC was also higher in former smokers. UC usually runs a more benign disease course in smokers compared to non-smokers with fewer flare-ups, decreased hospitalization rates, less need for oral steroids, and lower colectomy rates. An interesting link has been reported between smoking habits and the course of UC.
- Ever smoking was found to be associated with increased risk of CD development. Smoking also affects the disease course. Many studies report a higher prevalence of ileal disease and a lower prevalence of colonic involvement in smokers. Smoking was associated more frequently with penetrating intestinal complications and greater likelihood to progress to complicated disease, as defined by development of strictures or fistulae and a higher relapse rate
- Treatment with nicotine was tested clinically in UC. Initial trials showed the efficacy of nicotine delivered in transdermal patches in controlling active disease, but its failure to maintain remission



Smoking and other autoimmune diseases

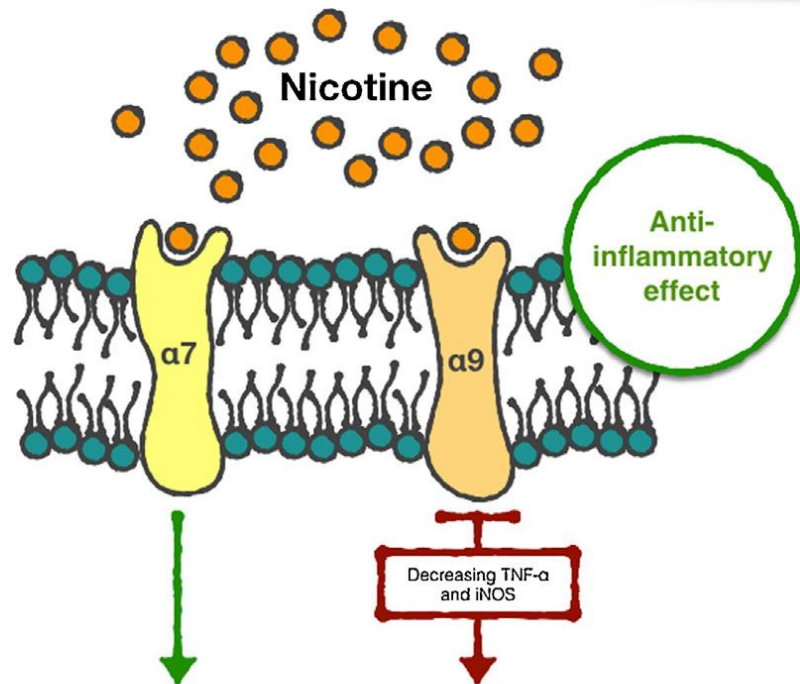
- Smoking has been demonstrated to accelerate the progression of primary biliary cirrhosis (PBC) and to be a risk factor for the development of the disease
- Smoking has been associated with a 40-80% increase in the prevalence of multiple sclerosis (MS). Cigarette smoking has been associated with a 3-fold higher risk of transforming or hastening the transformation of relapsing-remitting forms of the disease into progressive forms
- Some epidemiologic studies described an association between smoking and chronic widespread pain (CWP) and pain at certain body sites like the back, neck, shoulders, and legs
- Smoking is a risk factor for the development of Graves' hyperthyroidism (GH) and even more so for Graves' ophthalmopathy. Thiocyanate, a major component of smoke, derived from hydrogen cyanide, leads to increased excretion of iodine, inhibits iodine uptake by the thyroid, competes with iodide in the organification process, and inhibits thyroid hormone synthesis

Invited review

Nicotine and autoimmunity: The lotus' flower in tobacco

João Pedro Gomes^{c,d}, Abdulla Watad^{a,b}, Yehuda Shoenfeld^{a,b,*}

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Decreased pro-inflammatory cytokines
Promotes T cells apoptosis
Potentiates Treg suppressive effect

Impact on development and antibody secretion of B cells

Anti-inflammatory mechanisms of action of Nicotine.

Nicotine binds to 7 subunit of nicotinic acetylcholine receptor, promoting an anti-inflammatory effect. New findings demonstrated a different pathway; nicotine blocks 9 subunit, decreasing TNF and IL-1 production

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- **MS:** The neuro-protective mechanism of nicotine was previously described. Initially, it was declared that the protection effect on EAE was related to 7-nAChR binding of nicotine. However, others demonstrated that only partial anti-inflammatory response can be attributed to this subunit.
- **RA:** nicotine, a selective agonist of cholinergic anti-inflammatory pathway, has been suggested as a beneficial molecule in RA. The effect of intraperitoneal injection of nicotine every day after inducing the disease showing that nicotine can reduce joint swelling and pain, alleviate synovial inflammation and reduce bone destruction, through the activation of cholinergic pathway (animal study)
- **Behcet' Disease:** amelioration of mucocutaneous manifestations
- **Sarcoidosis:** a study using nicotine patches in patients with active pulmonary disease. After a 12 weeks of treatment, patients with stage II and III pulmonary active sarcoidosis did not report any clinical benefit, but they had increased Tregs levels and they presented a restored responsiveness of toll-like receptors 2 and 9.

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- **Ulcerative colitis:** A nicotine preparation (enema) was used in an open pilot study with patients with left colon active disease, refractory to first line therapy. Ten patients were admitted to this 4 weeks study, but three failed to conclude it. Seventy-one percent presented clinical and endoscopic improvements, but 40% referred transient and mild side effects **and none of them had histological improvement.**
- **Chron's Disease:** no beneficial effect

Considering the anti-inflamtry and addictive effects of nicotine products are important to us these products for treatment strategies.

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