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Circadian Deregulation as Possible New Player in Pollution-Induced Tissue Damage

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Abstract: Circadian rhythms are 24-h oscillations driven by a hypothalamic master oscillator that entrains peripheral clocks in almost all cells, tissues and organs. Circadian misalignment, triggered by industrialization and modern lifestyles, has been linked to several pathological conditions, with possible impairment of the quality or even the very existence of life. Living organisms are continuously exposed to air pollutants, and among them, ozone or particulate matters (PMs) are considered to be among the most toxic to human health. In particular, exposure to environmental stressors may result not only in pulmonary and cardiovascular diseases, but, as it has been demonstrated in the last two decades, the skin can also be affected by pollution. In this context, we hypothesize that chronodisruption can exacerbate cell vulnerability to exogenous damaging agents, and we suggest a possible common mechanism of action in deregulation of the homeostasis of the pulmonary, cardiovascular and cutaneous tissues and in its involvement in the development of pathological conditions.

Keywords: circadian clock; pollution; antioxidant system

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1. Introduction

The circadian machinery governs many human physiological functions that exhibit rhythmic variations over the course of the day, with the adaptive purpose of providing the optimum temporal organization of physiological processes in relation to the environment [1–3]. These changes are regulated by a central oscillator located in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus [4]. In humans, the central circadian pacemaker coordinates autonomous peripheral oscillators located in almost all tissues and organs, including the lung, heart and skin [5–7].

At a cellular level, the molecular circadian system consists of a transcriptional and translational feedback loop based on the CLOCK (Circadian Locomotor Output Cycles Kaput):BMAL (Brain and Muscle Arnt-Like protein 1) heterodimer, which activates the transcription of period (PER) and cryptochrome (CRY). In turn, the PER and CRY heterodimeric complex inhibits its own transcription by suppressing the CLOCK:BMAL transcriptional function [8]. The CLOCK:BMAL complex regulates Rev-Erb and Ror transcriptions, which modulate the timing and amplitude of Bma1 expression, forming a second stabilizing feedback loop [9]. In addition to the core clock components, the molecular oscillator also dictates the timing of tissues and cell-specific genes, referred to as clock-controlled genes (CCGs) [10]. These specific tissue and cell clock-controlled transcriptomes ensure the temporal regulation of physiological processes.

Circadian clocks have to be plastic, because most organisms, including humans, face different adaptive challenges every day. They have to cope with cyclical variations of

the physical properties of their environment, such as light intensity and temperature. A synchronized clock improves cellular homeostasis; in fact, evidence suggests that circadian arrhythmicity has detrimental consequences on human health [11,12].

Loss of synchronization between biological clock and external stimuli can be induced by the alteration of metabolic pathways as occurs in many diseases, such as cancers and age-dependent disorders [13,14]. Irregular schedules of life activity, such as work schedules that include long-term night shifts, rotating shift work, late-night activity or jet lag [15–17] induced by transcontinental travel, are an important disruptor of functional circadian synchronization. These changes in the day/night lifestyle are a consequence of the increase in modernization and industrialization that is characterized by world economic growth.

Starting from 1700, industrialization heavily affected the environment, with harmful effects on air quality. Global air quality results from the concentration of gaseous pollutants and particulate matters. As defined by Jacobson, "air pollution occurs when gases or aerosol particles emitted anthropogenically, build up in concentrations sufficiently high to cause direct or indirect damage to plants, animals, other lifeforms, ecosystems, structures, or works of art" [18].

The effects of short-term and chronic exposure to airborne stressors due to intensified industrialization and urbanization are well documented [19–21].

Even though the complicated mechanisms of the harmful health effects of airborne pollution are not fully clear, many epidemiological and clinical studies have demonstrated a correlation between exposure to pollutants and pathological conditions in tissues, such as lung dysfunction, cardiovascular diseases, skin conditions and, more generally, detrimental multi-organ effects [22–25]. Although pollution is defined by a single word, its meaning includes a wide range of compounds that have been recently classified by the EPA into six different groups: particulate matters (PMs), nitrogen oxides (NO), sulphur oxide (SO), carbon monoxide (CO), heavy metals and tropospheric (ground-level) ozone (O_3) [26]. Among them, PMs and O_3 have been considered among the most relevant to our modern time, as their tropospheric concentration is in constant increase. PMs emitted from vehicles, construction sites, industries and burning of fossil fuels include different inhalable suspended particles, which, based on their size, are divided into PM_{10} (with an aerodynamic diameter < 10 μm), $PM_{2.5}$ (with an aerodynamic diameter < 2.5 μm) and UFP (ultrafine or nanoparticles, $\leq$0.1 μm) [27]. In a recent work conducted in 652 different cities of the six different continents, a significant correlation between PMs exposure and all-cause mortality has been demonstrated in countries with a high annual mean temperature and a limited management of the environment [28].

As mentioned above, another relevant air pollution compound is the tropospheric O_3, defined as a secondary pollutant, since it is formed through chemical reactions from precursors (volatile organic compounds, nitrogen oxides, carbon monoxide) in the presence of sunlight [29]. Over the last ten years, the World Health Organization (WHO) has reviewed many studies on the effects of acute O_3 exposure on human health [30], ranging from the respiratory to cardiovascular [31] systems, including the central nervous system [32]. In particular, it is well known that acute O_3 exposure affects pulmonary function, inducing throat irritation and consequently, coughing, and worsening the health conditions of asthmatic people [33]. Moreover, a clear deterioration of the olfactory function as a consequence of acute exposure to 0.2 ppm O_3 in healthy subjects has been recently documented [34]. Concerning the chronic effects of O_3 [35], it has been demonstrated that long-term exposure to O_3 is significantly associated with increased mortality for cardiovascular or ischemic heart disease, respiratory pathologies or chronic obstructive pulmonary disease.

Since PMs and O_3 exposure mainly occur by inhalation, the deleterious effects of both environmental stressors have been widely studied, especially on the pulmonary and cardiovascular systems. However, researchers have recently focused their attention also on the impact of airborne pollution on skin conditions not limited to premature aging, but also to proinflammatory diseases such as dermatitis, eczema, psoriasis and rash [36–38].

Despite the different mechanisms underlying air pollutant-induced diseases, oxidative stress has been recognized as a unifying feature of their toxic effects.

Based on this evidence, this review intends to focus on the synergic connection of circadian clock desynchronization and environmental pollutant toxicity. In this regard, this paper summarizes a panel of data concerning the deleterious effects of both exposure to environmental stressors, and chronodistruption on three body regions which are considered the principal targets of air pollution: the pulmonary, cardiovascular and cutaneous systems. Finally, we identify the antioxidant defense system of the tissue as a possible link between these aspects. Until now, to the best of our knowledge, research has focused on how environmental pollution affects circadian rhythm, and how circadian rhythm affects the toxicity of environmental stressors. Here, we explore the topic using a different perspective, since we hypothesize that circadian deregulation exacerbates the detrimental effects of airborne pollution as a result of less efficient defensive redox machinery.

A comprehensive literature review identified 141 papers published (between 2000 and 2021, except [29,39,40]) in peer-reviewed scientific journals, books, or available on scientific internet sites. This work was centered on a systematic search in the PubMed and Google Scholar databases by the following specific keywords or combinations of them: circadian clock; pollution; oxidative stress; circadian clock deregulation; oxidative stress and cardiovascular system; oxidative stress and pulmonary system; oxidative stress and skin; oxidative stress and circadian clock; pollution and circadian clock; antioxidant system and pollution; circadian system and antioxidant defenses.

2. Detrimental Health Effects of Circadian Desynchronization in the Pulmonary System

Since the concentration and composition of air pollution show strong correlations to the time of the day, with the ozone peak later in the noon hours [41,42], and also diurnal trends in the concentration and composition of PMs [41,43], a defense system able to anticipate the diurnal variation of environmental pollutants provides fitness advantages to organisms. In this light, the circadian system plays a critical role in lung tissue defense against outdoor stressors [39,44–46].

Air pollutants, allergens, pollens, cigarette smoke, as well as respiratory viral and bacterial infections can lead to the onset of acute diseases, and in parallel, to the worsening of chronic pathologies like COPD (Chronic Obstructive Pulmonary Disease) and asthma [40,47–49]. In physiological conditions, the circadian system modulates several lung functions, such as airway caliber and resistance, respiratory symptoms, mucus secretion and immune-inflammatory responses; however, circadian disruption has been associated with several chronic and acute airway conditions [50,51]. Moreover, circadian desynchronization can boost lung tumorigenesis, as demonstrated in a recent work by Papagiannakopoulos et al. [52] where the tumor-suppressive role of the core clock genes Per2 and Bmal1 was established. Clock dysregulation is also responsible for alterations in various cellular and molecular lung functions during the pathogenesis of chronic airway disease. As mentioned above, a link between the circadian timing system and the worsening of lung function, observed in both COPD and asthma, has been widely demonstrated [5,46,50,53–55]. Particularly, a growing number of studies show the role of clock perturbation in pulmonary physiology and pathology in response to pollutants. In rodents, alteration of pulmonary clock gene expression induced by air pollutants and proinflammatory agents like LPS and TNF-α has also been shown [56].

The interconnection of chronic inflammatory lung diseases, circadian function and oxidative stress is established by the link between the molecular clock and NF-κB and Nrf2 pathways, particularly in the case of pulmonary responses to environmental pollutants, viruses and bacteria [5]. The circadian system may act under normal circumstances as a modulator of lung inflammo-immune responses that, when challenged (as in response to a pollutant), can also act to increase the amplitude and extent of proinflammatory impact on pulmonary function [5].

Understanding the mechanism whereby the arrhythmic circadian clock influences lung pathophysiological functions could lead to new and effective ways for treatment based on chronopharmacological agents. This knowledge highlights the need for the development of novel strategies that act on the circadian molecular clock for the treatment of pulmonary disorders, and that also account for the rhythmic variation of lung function across the 24-h day.

3. Detrimental Health Effects of Circadian Desynchronization on the Cardiovascular System

In humans, most cardiovascular (CV) functions exhibit circadian variations, including heartbeat dynamics [57], cardiac vagal modulation [58], platelet aggregability [59] and plasminogen activator inhibitor 1 (PAI-1) [60,61].

These rhythmic and predictable-in-time oscillations of cardiovascular functions are guaranteed by a fine-tuned regulation of the circadian system. Thus, circadian variation in the physiology of the cardiovascular system leads to daily rhythmicity in the susceptibility and occurrence of pathological events. Indeed, epidemiological studies report a morning peak in cardiovascular failures, largely attributable to the fact that the circadian system influences CV risk factors [62].

As synchronized circadian rhythms contribute to CV well-being [63], circadian misalignment may influence CV risk. Chronodisruption leads to physiological alterations that are linked with CV disease, such as an increase in both systolic and diastolic blood pressure, alteration of daily rhythmicity of heart rate, disruptions to the rhythmic urinary epinephrine and norepinephrine excretion rates, and increased serum levels of inflammatory markers, including interleukin-6, high-sensitivity C-reactive protein, resistin and TNFα [62]. These alterations have negative consequences on hemodynamic function [64–66], arterial stiffness [67] and thrombogenic pathways [66]. Moreover, circadian desynchronization has directly been related to cardiomyopathy [65,68,69], coronary artery disease [70] and stroke [71]. An association between shift work and CV disease has been proven [72], further supporting the hypothesis that circadian misalignment (typical in night-shift workers) negatively alters CV risk factors.

Recent investigations focus on the role of circadian machinery in the modulation of oxidative stress pathways, which are often involved in heart disease outcomes. In particular, Khaper et al. [73] suggested a key novel relationship between the circadian system and oxidative stress after myocardial infarction (MI). It is well established that circadian rhythms regulate healing after MI, and circadian desynchronization contributes to adverse cardiac remodeling post-MI [74]. Moreover, melatonin seems to have a cardioprotective role beside its free radical scavenging properties [75].

This evidence supports the hypothesis that the circadian clock plays an important role in regulating oxidative stress pathways that can potentially contribute to cardioprotection. Furthermore, considering the ability of pollution to affect tissue redox homeostasis, it is possible that pollution affects cardiovascular conditions also via the deregulation of the circadian clock.

4. Detrimental Health Effects of Circadian Desynchronization on Skin

The largest organ of the human body, the skin, is the first barrier of protection against external stressors. Different skin functions have been shown to follow a strong circadian rhythm, optimized for more protection during daylight and for repair during nighttime [76]. Synchronization to environmental time cues is crucial for optimal benefits to the skin. A recent work emphasized the importance of the circadian clock in regulating skin functions [77]: predictable daily periodicity has been reported in humans in skin cell proliferation rates, cellular senescence, epidermal barrier function, hydration and transepidermal water loss, capillary blood flow, sebum production, temperature, surface pH and the appearance of wrinkles [76,78,79]. Regulated circadian activities allow the skin to adapt its functions to variations in environmental conditions.

The impact of a deregulated circadian clock on the development or, at least, the progression of several pathologies has been shown [11,12]. Studies have suggested the role of clock synchronization in protecting the skin from exogenous stressors [7]. In particular, several proinflammatory cutaneous conditions (such as psoriasis, eczema, cutaneous rashes, and atopic dermatitis) have been attributed to environmental factors, such as O_3 [80,81]. In a recent study, our group has suggested that a synchronized circadian clock not only facilitates the protective role of the defensive pathway in terms of a faster and more efficient antioxidant response against environmental insults, but also moderates the cellular damage resulting from chronic inflammation [82].

Moreover, the data showed a link between the circadian clock and skin aging: arrhythmic Bmal1 mutant mice exhibit accelerated skin aging, probably related to oxidative stress that generated an unbalanced redox homeostasis [83,84]. An epidemiological study by Li et al. [85] on the association of shift work with increased risk of psoriasis suggests the possibility that lifestyle changes and consequent circadian disruption could be involved in many skin diseases.

5. Effects of Pollution on the Respiratory Tract

Several experimental data correlate both acute and long-term exposure to air pollutants with changes in lung function. Environmental stressors are associated worldwide with hospitalization for respiratory disease and, in particular, close links with particulate matter, $PM_{2.5}$, PM_{10}, and O_3 have been demonstrated [86,87]. During pulmonary ventilation, these pollutants could induce an increase in respiratory dysfunction, such as asthma, COPD and lung cancer [88]. In more detail, older people, infants or subjects with comorbidities [89–91] seem to be more vulnerable to the harmful effects of airborne pollution.

The correlation between COPD and increased levels of PM_{10} and $PM_{2.5}$ in the air is well documented. In the last decade, Gan et al. demonstrated that exposure to high levels of air pollutants resulted in a noticeable increase in COPD hospitalizations and mortality in a Canadian population sample [92]. These data confirmed previous studies conducted in several US cities [86,93]. There is also evidence concerning the European population; in particular, different studies associate respiratory infections during early childhood to particulate matter concentration [90,94–96].

The noxious action of tropospheric O_3, due to its low solubility in water, is carried out in the inner layer of the respiratory tract, where it reacts with epithelial lining fluid which protects the alveolar structures from external stressors and pathogens [97,98].

Just in the last year, several human studies have recognized significant associations between both short-term and chronic exposure to O_3 and hospitalizations for decrease in lung function due to increased airway inflammation, respiratory illness, aggravation of asthma and even for COPD [99–101], but the data concerning the susceptibility of populations are still unsatisfying.

In a meta-analysis study conducted by Bell and colleagues [102], a direct association between short-term O_3 exposure and age has been suggested, and elderly populations seem to be more sensitive to this specific airborne stressor. On the other hand, it was demonstrated that children are more vulnerable to O_3 and, especially among children who live in industrial zones, O_3 exposure is significantly associated with wheezing and allergic rhinitis [103,104].

Concerning the mechanism by which external pollutants trigger or exacerbate pulmonary system diseases, in vitro and in vivo evidence suggests that they have the intrinsic ability to induce oxidative stress [97,105]. In particular, the toxic effects of pollutants result both from increased exposure to oxidant components (i.e., ROS), and from impairment of the antioxidant defense system, which initiates a number of redox-sensitive signaling pathways that play a key role in pulmonary inflammatory response [106].

6. Effects of Pollution on the Cardiovascular System

Due to the close connection between the respiratory and cardiovascular systems, airborne pollutants are not only associated with altered lung functions, but also with cardiovascular morbidity. Evidence has been accumulated indicating that environmental stressors negatively affected cardiovascular function, in terms of increases in heart failure events, arrhythmias, myocardial infarction, stroke and reduced survival after stroke [107].

Some evidence indicates that particulate matters, in particular $PM_{2.5}$, unsafely affect the cardiovascular system, inducing events occurring within a short or long time after exposure [108]. Exposure to PMs can induce acute cardiovascular events, such as heart arrhythmias, stroke or myocardial infarction, [109] while long-term exposure amplifies the risk of heart failure [110].

Concerning O_3, there is a large amount of epidemiological evidence on the burden of short-term exposure on cardiovascular functionality and associated mortality. In a very recent work conducted on 67 volunteers, it was demonstrated that O_3 exposure altered blood pressure and heart rate, or more generally, affected autonomic function. In the same study, the authors established that short-term exposure to O_3 also induces systemic inflammation and oxidative stress, and alters hemostasis in terms of activation of fibrinolysis [111].

With reference to the chronic effects of O_3 exposure and cardiovascular outcomes, the evidence is instead limited and controversial, although a substantial alteration in circulating biomarkers of oxidative stress, inflammation and coagulation has been demonstrated [112].

In a recent prospective US cohort study, with an extensive follow-up period of 17 years [35], long-term exposure to O_3 was significantly associated with increased cardiovascular disease mortality or ischemic heart disease.

As mentioned for the respiratory tract, there is increasing evidence that indicates reactive oxygen species (ROS)-dependent pathways as common threads in the mechanism of action of external stressors on cardiovascular tissues [113–116].

Davel and colleagues [117] demonstrated that in adult Wistar rats, $PM_{2.5}$ induced vascular oxidative stress and augmented the expression level of two pivotal antioxidant enzymes in vascular tissue: Cu/Zn- and Mn-superoxide dismutase. The authors suggested that the enhanced expression of these two isoforms of superoxide dismutase represents a protective cellular mechanism induced by $PM_{2.5}$ exposure.

In an interesting study by Kodavanti and colleagues using a murine model, it has been demonstrated that episodic exposure to external stressors induced vasoconstriction in the aorta associated with a marked mRNA upregulation of biomarkers of oxidative stress [118]. They also observed that cardiac mitochondrial phospholipid fatty acids diminished after exposure to injurious particles, resulting in oxidative modifications.

7. Effects of Pollution on Skin

Besides the pulmonary and cardiovascular systems, the skin, due to its critical location, is one of the most susceptible tissues to the deleterious effect of airborne pollutants [119,120].

External pollutants can clearly affect skin homeostasis by acting in different ways. Concerning O_3, as discussed by Pecorelli et al. [37], it cannot penetrate cutaneous tissue, but its toxicity is a consequence of the interaction with the lipids present in stratum corneum (the outermost layer of the epidermis), leading to the generation of bioactive molecules (i.e., lipid peroxidation) that can then affect the deeper layer of the skin [121–123]. Conversely, PMs can move (although still under debate) through the different layers of the skin, inducing nuclear translocation of the transcription factor NFκB, increasing levels of HNE and promoting DNA damage [124–126].

Besides these differences, we can identify a common denominator in their mechanism of action, which is represented by an altered oxidative homeostasis and peroxidation that can lead to inflammation and exacerbation of pre-existing cutaneous diseases and/or premature skin aging. Although the skin is prepared for this injury with solid and valid an-

tioxidant systems (vitamin C, lipoic acid, vitamin E, carotenoids, or enzymatic antioxidants, such as catalase, dismutase, superoxide dismutase, glutathione peroxidase), their efficiency decreases with age, making the skin more susceptible to damage induced by exposure to airborne pollutants [127].

As a consequence, outdoor stressors are strictly associated with several skin conditions, including cancer [128]. One of the first epidemiological studies conducted by Vierkotter and colleagues in the SALIA (Study on the influence of Air pollution on Lung function, Inflammation and Ageing) cohort demonstrated that the danger of forming age spots or coarse wrinkles increased, in particular, by exposure to high levels of background traffic-related PMs. Moreover, the authors concluded that skin ageing is more evident in women [129].

The link between PMs and inflammatory skin diseases was also described, although the impact of external pollution on the development of atopic skin pathologies is controversial [130]. It is now clear that exposure to air pollutants exacerbates the manifestations of inflammatory skin pathologies, such as psoriasis, dermatitis or acne in both childhood and adults [119].

A large amount of evidence demonstrated that the harmful effect of O_3 exposure on skin tissue correlated with increasing emergency-room visits for eczema, urticaria, contact dermatitis, nonspecific eruption and other skin disorders [80].

Finally, the mechanism involved in the correlation between O_3 exposure and inflammatory cutaneous disease has been described recently [131]: O_3 can stimulate the activation of the well-known inflammasome in a redox-dependent manner, proposing a conceivable role of this pathway in O_3-induced inflammatory skin diseases [132].

To date, a number of biological mechanisms and intracellular pathways could be associated with adverse human outcomes as a result of exposure to airborne pollutants; indeed, great progress has been made in establishing that exposure to external stressors induces oxidative stress and inflammation.

8. Conclusions

Disturbances to the circadian rhythm and worsening of air quality are an integral part of environmental responses to technological progress and industrialization [133,134]. Despite this, the majority of environmental studies have not taken into account the impact of exposure to air pollution on human health, in a condition where the rhythmic circadian clock is dysregulated—today a very frequent situation as a result of modern lifestyles.

At present, studies on pollution-induced tissue damage correlated to circadian biology focus on two different aspects: how exposure to air pollutants disturbs the molecular clock [5,135], and how circadian rhythms influence susceptibility to external stressors throughout the day [136].

To fill the gap in knowledge on this topic, our review investigates whether circadian desynchronization increases susceptibility to ozone and particulate matter, two of the principal air pollutants affecting pulmonary, cardiovascular and cutaneous systems, which are among the principal targets of pollution-induced damage.

We believe that the intersection of the circadian clock and environmental pollution susceptibility could be traced back to the efficiency of the antioxidant system in free radical detoxification processes.

It has been shown that O_3 and PMs, even if they are two different injurious agents, can trigger the formation of reactive oxygen species (ROS), leading to deleterious effects on different human tissues [23,27,31]. In particular, overexposure to airborne pollutants causes a cellular redox imbalance between ROS generation and nonenzymatic and enzymatic antioxidant systems, with a consequent disruption of tissue homeostasis [137].

Desynchronization of the circadian clock has previously been associated with augmented sensitivity to air pollution exposure in the cardiovascular tissue of mice. In particular, the sensitivity to inhaled nanoparticles in Bmal1$^{-/-}$ mice increased,

compared to Bmal1$^{+/+}$ mice. After exposure to air pollutants, the antioxidant cellular defense system is less efficient in clock-deficient mice [138].

Moreover, the role of clock synchronization in protecting human tissues from environmental injury has been properly described. In particular, it has been shown that in clock-entrained human keratinocytes exposed to oxidative stressors, the activation of NRF2, the key master of the antioxidant pathway, is faster and more efficient compared to arrhythmic cells [7,82].

Starting from this evidence, we speculate that chronodistruption triggered by industrialization and modern lifestyles can exacerbate cell vulnerability to exogenous damaging agents, reducing the performance of the antioxidant system, and contributing to a worsened health state.

To conclude, the link between balanced redox homeostasis and the deleterious effects of airborne pollutants on the circadian system underlines the importance of a sustainable development and proper management of air quality standards to ensure healthy lives and to promote human well-being (Figure 1).

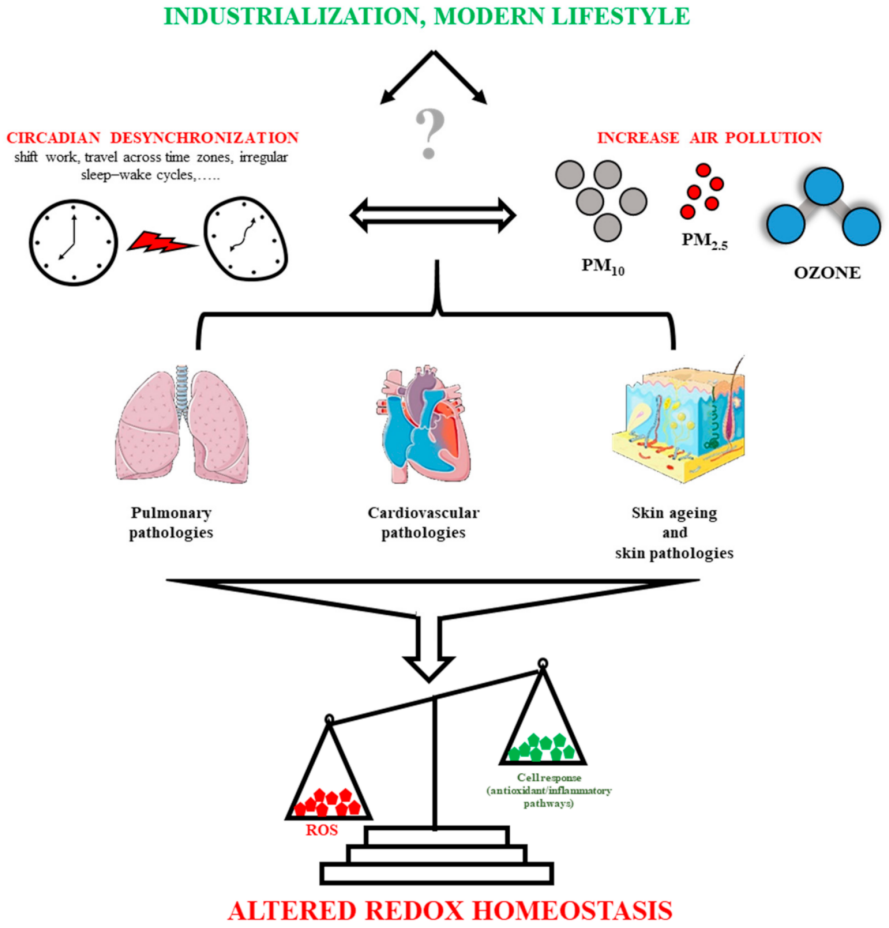

Figure 1. Schematic summary of the conclusion section. In this review, we summarize the negative impact of the environmental stressors (in particular, ozone and particulate matters) and desynchronization of the circadian system on pulmonary, cardiovascular and cutaneous systems. We hypothesize that circadian misalignment can exacerbate cell susceptibility to airborne pollutants, reducing the efficiency of the antioxidant defense system, and worsening the state of health.

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