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Chronic age-related diseases share risk factors: do they share pathophysiological mechanisms and why does that matter?

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Summary

The World Health Organization (WHO) assigns high priority to the prevention of non-communicable age-related diseases such as heart disease, cancer, diabetes, stroke and chronic lower respiratory diseases. They are now the leading causes of death, in both industrialised and developing countries, mostly due to increased life expectancy and urbanisation with associated changes in lifestyle and environment. Tobacco smoking, physical inactivity and resulting obesity are established risk factors for many chronic diseases. Yet, the aetiology of age-related diseases is complex and varies between individuals. This often makes it difficult to identify causal risk factors, especially if their relative effects are weak. For example, the associations of both obesity and air pollution with several age-related diseases remain poorly understood with regard to causality and biological mechanisms. Exposure to both, excess body fat and particulate matter, is accompanied by systemic low-grade inflammation as well as alterations in insulin/insulin-like growth factor signalling and cell cycle control. These mechanisms have also been associated in animal and some human studies with longevity and ageing in more general terms. In this paper, it is therefore hypothesised that they may, at least in part, be responsible for the adverse health effects of obesity and air pollution. It is argued that molecular and genetic epidemiology now offer novel instruments to improve the understanding of these pathophysiological pathways and their link to disease aetiology. Understanding the causality of exposure disease associations and differences in susceptibilities to environment and lifestyle is an important aspect for effective prevention.

Key words: *pathway; obesity; air pollution; public health; systemic inflammation; insulin; insulin-like growth factor; cell cycle; genomics*

Non-communicable age-related diseases – a global challenge

The World Health Organization (WHO) assigns high priority to the prevention of chronic diseases in all parts of the world [1]. Non-communicable age-related diseases (NCDs) such as heart disease, cancer, stroke and chronic lower respiratory diseases are now the leading causes of death, in both industrialised and developing countries. From the perspective of society, the increase in average life expectancy, living in an urban environment and the westernisation of lifestyle are the most important risk factors for the global increases in NCD morbidity and mortality. At the centre of strategies to improve the health of people must be behavioural and environmental risks, as these can be modified [2]. Yet, the aetiology of NCDs is complex and varies between individuals. This often makes it difficult to identify causal risk factors, especially if their relative effects are weak (i.e. air pollution, passive smoking). The expectations for molecular epidemiology and genetics in chronic disease epidemiology are to improve the understanding of causality in exposure-disease associations as well as of disease susceptibilities. In addition, they will help elucidate the biological mechanisms underlying diseases, as well as the adverse health effects of exogenous risk factors [3–5].

Age-related diseases share risk factors: do they share pathophysiological pathways?

No longer can each chronic illness be considered in isolation. Awareness is increasing that they share common, usu-

ally related risk factors, and that integrated strategies can be effective for many different conditions [6].

Understanding common risk and disease patterns, as well as their causal links and underlying biological mechanisms, is important for public health. It helps target prevention to causal aspects of lifestyle and environment that are generally unhealthy. This strengthens strategies to increase the amount of life spent in good health [7–9]. The hypothesis of shared aetiologies between diseases is supported by evidence, that the presence of one chronic disease in a person is often associated with an increased risk for developing additional health conditions [10–11]. Results from genetics and genomics also suggest that diseases are not as independent of each other as was believed in the past [12–13]. A paradigm shift in disease categorisation is taking place. Efforts are under way to systematically link all genetic disorders (the human "disease phenome") with the complete list of disease genes (the "disease genome") [12–13]. They offer the opportunity to identify general patterns underlying human health and disease. Unfortunately, these efforts to identify the "diseasome" of all known disorder and gene associations largely ignore the social and physical environment in which humans live and function [12–13]. This is a severe limitation, as only modifiable risk factors can be the target of prevention.

Systemic inflammation, insulin resistance, and alterations in cell cycle control: public health-relevant disease mechanisms?

Different biological mechanisms and genes have been associated with more than one disease or risk factor. This paper focuses on the hypothesis that systemic inflammation, insulin resistance and alterations in cell cycle may potentially belong to the many public health-relevant pathophysiologies. The reasoning is based on two globally important risk factors with broad adverse health effects, namely obesity and air pollution. Both have important links to systemic inflammation, oxidative stress and insulin resistance. However, whether these mechanisms are only biomarkers of exposure or active players in disease causation is still debated in several circumstances. Resolving the question of causality will have important implications for prevention.

How obesity may shorten life

According to observational studies, obesity is a major determinant of premature mortality and a risk factor for the most significant causes of death such as type II diabetes, cardiovascular disease and various types of cancer [14–15]. Although in some cases, being overweight is also known to protect against age-related health problems such as bone fractures and osteoporosis [16]. A large retrospective study on the long term impact of gastric bypass surgery showed that weight loss was associated with a decrease in overall mortality as well as in mortality due to diabetes, heart disease and cancer, whereas mortality due to other causes such as accidents and suicide was increased in the treatment group [17–18]. Despite the broad evidence on the diverse health effects of obesity, many open questions remain regarding its association with chronic diseases. The causality of the association with specific diseases, such as some types of cancer or asthma, is still debated. From a public health perspective, it is important to weigh the adverse overweight effects against some of its protective effects. The relevance of different obesity markers is the focus of ongoing research. Finally, the pathophysiological mechanisms underlying the health effects of obesity remain to be fully elucidated [19]. Systemic low-grade inflammation and insulin resistance are two related mechanisms hypothesised to play a role in at least part of the obesity-disease associations. They are also present in many obesity-associated chronic diseases, including type 2 diabetes, hypertension, cardiovascular disease as well as some types of cancer [20–21], but the causality of all these interrelationships is often unclear [22].

Insulin/IGF-1 signalling: association with obesity, caloric restriction and longevity

Obesity, especially visceral adiposity, is associated with insulin resistance. In insulin resistance, serum levels of insulin and insulin-like growth factors are elevated and insulin/IGF-1 signalling is altered. Insulin resistance plays a physiological role in the pre- and postnatal period for growth stimulation. However, after puberty, IGF-1 serum levels decline. Persistent insulin resistance in late adolescence and adulthood is a risk factor of chronic diseases [21, 23] and may well be one of the key pathophysiological mechanisms mediating the adverse health effects of a western lifestyle and environment.

The impact of long-term caloric restriction on lifespan and decreased incidence of both neoplastic and non-neoplastic lesions in mammals has been attributed, in part, to alterations in insulin/IGF-1 signalling [24]. Clearly, the mechanisms underlying the impact of caloric restriction are complex and not fully understood. However, it has been found that circulating levels of anabolic hormones and hormones that regulate thermogenesis and cellular metabolism are lower. Animals with restricted energy intake cope better with a broad array of acute stressors. They exhibit enhanced DNA repair, probably through an adaptation called hormesis. However, alterations of insulin/IGF-1 signalling and associated systemic inflammation are, potentially, also very important in mediating the effect of caloric restriction [20], as reduced IGF-1 signalling promotes longevity in several animal models. This effect has been attributed, in part, to a decreased occurrence of several age-related diseases.

Humans who live to an old age are less likely to exhibit insulin resistance. Metabolic characteristics promoted by caloric restriction in humans living to very old ages include low circulating levels of fasting plasma glucose, insulin, free insulin and IGF-1 levels. Long-term calorie restriction without malnutrition is also associated with decreased levels of oxidative markers in blood and urine and protects against systemic inflammation [25–26]. Yet, in general, the effects of caloric restriction in humans are inconsistent and are likely to be complex [20, 27–28]. The impact of long-

term caloric restriction accompanied by adequate nutrient supply on the burden of chronic diseases in humans remains to be proven [20] and must be carefully weighed against some of the beneficial health effects of being overweight, especially at higher age.

Systemic low-grade inflammation: its links to obesity, insulin/IGF-1 signalling and cell cycle control

Chronic inflammation and reactive oxygen species damage molecules, tissues and organs, and are a key feature of ageing and many chronic diseases [25–26]. Many markers associated with biological ageing are related to chronic inflammation, such as serum levels of IL-6, IL-1beta or TNF-α [25–26]. Elderly subjects exhibit higher circulating levels of pro-inflammatory molecules in their circulation. Blood concentrations of these pro-inflammatory substances during childhood and adolescence are predictive of morbidity and mortality in adulthood. It has been hypothesised that systemic subclinical inflammation may, in part, reflect ageing processes of the immune system. Chronic or repetitive infections and lifelong exposures to antigens decrease the efficiency of immune cells in fighting invaders over time. Possibly in reaction to this decreased effectiveness, apoptosis of immune cells, particularly neutrophils, diminishes and leads to the overproduction of oxidative substances [23, 26, 29].

It is well established that inflammatory and insulin/IGF-1 signalling pathways interact [23, 30]. Subclinical inflammation, such as in obesity or related to other chronic disease risk factors, increases insulin resistance [30–31]. Adipokine production in obesity is abnormal and some pro-inflammatory signalling pathways are induced. The white adipose tissue of obese persons produces pro-inflammatory cytokines including TNF-α and IL-6 in excess, possibly due to the infiltration by macrophages. These changes in cytokine production by adipocytes and macrophages are believed to contribute to obesity-related insulin resistance [23].

The link between systemic low-grade inflammation and insulin/IGF-1 signalling is biologically meaningful. Insulin and IGF-1 are both potent mitogens, stimulate cell proliferation and are anti-apoptotic. By modulating their action in response to inflammatory mediators, tissue damage can be diminished. Inflammatory processes and resulting oxidant radicals damage DNA, lipids and proteins. As our body is continuously exposed to these highly reactive and electrophilic compounds, it had to develop defence mechanisms to prevent excessive tissue damage. Anti- and pro-inflammatory cytokines therefore interact with numerous signalling pathways that modulate the cell cycle, cell proliferation and apoptosis. Receptors involved in the immune response trigger transduction pathways that activate the phosphorylation process and transcriptional factors. Pro-inflammatory cytokines are thereby able to alter insulin/IGF-1 signalling [30, 32–33]. Protein kinases IKKb and JNK, as well as associated transcription factors NF-kB and AP1, are involved in the inhibition of phosphorylation of insulin/IGF-1 signalling, respectively. Both pathways are activated in obese subjects in response to adipokines, free fatty acids and oxidative stress [33].

Insulin/IGF-1 receptor signalling activates the PI3K/Akt kinase cascade which can then either activate or inhibit the function of several downstream pathways [34–35]. PI3/Akt signalling through FoxO (forkhead box group O) or NF-kB transcription factors is one of the key regulators of survival and mitosis. It plays a central role in cell cycle initiation, stress resistance and ageing [34–36].

Evidence from genetic studies on longevity: the link to systemic inflammation, insulin/IGF-1 signalling and cell cycle control

Even though longevity, ageing and susceptibility to age-related diseases are not exchangeable characteristics of human populations, approaches of systems biology to study protein-protein interactions have identified substantial overlaps between common signature networks of genes and proteins associated with longevity and major age-related diseases [8]. These common signature networks are enriched with signalling proteins. They point to several pathways of potential relevance to both longe-vity and chronic diseases, such as pathways associated with cell-cell and cell-extracellular matrix interactions, focal adhesion, and the adherens junctions [8]. They also include the insulin/IGF-1 signalling cascade with its tight links to adiposity and systemic inflammation [8, 20, 27].

Results from a recent genome wide scan for longevity determinants in the Framingham cohort [34], as well as from several candidate gene studies [36–42], provide strong support for the central role of insulin/IGF-1 and PI3/Akt signalling in longevity. FoxO gene variants have been identified as determinants of longevity in several of these studies.

FoxO transcription factors exhibit different physiological functions including regulation of cell cycles and growth, apoptosis, DNA repair and resistance to oxidative stress. They codetermine lifespan in C. elegans and Drosophila [36, 43–44]. Malfunctions in FoxO genes are involved in various cancers, insulin resistance, altered immune responses and organ damage [36]. FoxO transcription factors are involved in the regulation of whole body energy metabolism and glucose homeostasis and accordingly in insulin resistance [34–35, 44]. They induce the expression of several antioxidative and stress resistance genes and have a critical role in regulating the immune system [34–35]. Depending on the type of activation, they can exert diverse and even opposite effects [25, 45–46]. FoxO genes are negatively regulated by the PIK3/Akt pathway. In response to stress, specific FoxO genes may be further silenced by the SIRT1 gene [25, 34–35]. SIRT1 is itself a regulator of insulin/IGF-1 signalling and is known to down regulate p53-mediated senescence via deacetylation [25, 47]. Caloric restriction leads to an increase in SIRT1 activity [48]. Both, sirtuins and FoxO genes are evolutionarily conserved [42].

While insulin/IGF-1 signalling down-regulates the expression of FoxO transcription factors, it is known to activate NF-kB signalling and to thereby potentiate inflam-

matory responses, prevent autophagic clearance of cellular waste, and inhibit apoptosis of senescent cells [34–35]. The SIRT1 and SIRT6 longevity-related transcription factors can repress NF-kB signalling [34–35]. Thus the NF-kB and FoxO signalling pathways are important counter players in ageing and senescence. Excessive insulin/IGF-1 signalling blocks the FoxO branch of PI3/Akt signalling, and conversely activates the NF-kB branch [34–35].

The evidence presented above suggests that systemic low-grade inflammation, through pathways that include insulin/IGF-1 signalling, may be a key link between longevity, ageing and chronic diseases, as these mechanisms are tightly linked to the regulation of cellular and tissue fate [25].

Air pollution: a global disease risk factor potentiating the adverse effects of obesity and insulin resistance?

We hypothesise that systemic low-grade inflammation, insulin/IGF-1 signalling and downstream pathways including cell cycle control may mediate the effect of other chronic disease risk factors with inflammatory properties. The question arises whether such risk factors may even potentiate the health consequences of the obesity epidemic. This seems of particular relevance for air pollution, which is reaching epidemic dimensions in parallel to obesity and urbanisation [30, 49–50]. The strong inflammatory properties of air pollutants, and especially of particulate matter (PM), are well established [25] and may explain the multiple effects of these inhaled toxicants on different organs and diseases including the lung, the cardiovascular system and the brain [32, 51–54].

Considering the inflammatory properties of air pollution, and given the interaction between systemic inflammation and insulin/IGF-1 signalling, what is the evidence for an aetiological effect of PM on insulin resistance and the metabolic syndrome? The prevalence of these conditions is also dramatically increasing on a global scale, in parallel to obesity, air pollution and urbanisation [21, 30]. While evidence on the inflammatory properties and effects of PM is abundant [55–57], evidence for the association between air pollution and the metabolic syndrome is more limited [32, 53, 54, 58, 59]. Several studies have demonstrated that type 2 diabetics are more sensitive to the PM impact on heart rate variability [59]. Recently, Sun et al. [32] demonstrated that ambient PM2.5 potentiated the effect of obesity on insulin resistance, visceral adiposity, and inflammation in a diet-induced murine model. Particle exposure was shown to alter PI3K/Akt signalling in the aorta of the animals. The data suggest that the previously observed link between PM exposure and type 2 diabetes [53–54] may in fact be mediated by the exaggeration of insulin resistance and visceral inflammation due to PM. Knuckles and colleagues [60] studied changes in the transcriptome and transcription factor proteome of rat neonatal cardiomyocyte (RCM) cultures following an acute exposure to bio-available constituents of PM2.5 oil combustion particles. Genomic alterations observed included insulin/IGF-1 and PI3/AKT signalling and suggest an impact of the particles on cardiac myocyte electrophysiological remodelling, cellular oxidative stress and apoptosis. Diesel exhaust emissions can activate redox-sensitive transcription factors including NF-kB and AP1, both linked to insulin/IGF-1 signalling.

The PI3K/Akt pathway, which is in part regulated by insulin/IGF-1 signalling as outlined above, plays a key role in cell cycle progression, although the detailed mechanisms are still poorly understood [61]. It is of interest to note that cycle control emerged as one of the mechanisms being represented in several chronic diseases, following Cluett and colleagues' [7] review and comparison of findings from genome-wide association studies across different age-related disorders such as cardiovascular disease, cancer, type 2 diabetes, osteoporosis and dementia. A key role of cell cycle control is meaningful from an evolutionary perspective. Senescence seems particularly important in the protection against tumour development in an environment that continuously exposes the human organism to oxygen-derived radicals that damage DNA. However, cell cycle control genes involved in tumour biology may also be of relevance to other inflammation and oxidative stress- related diseases, as they regulate senescence and therefore tissue remodelling beyond an impact on DNA repair [25].

Inflammation and tissue remodelling are key characteristics of several chronic airway diseases. Several lines of evidence imply altered expressions of cyclin-dependent kinases (CDK), which are key players in cell cycle control, in emphysema, impairment of lung function, and tissue remodelling in the lung [25]. PM has been found to alter the regulation of G1 cyclins and CDKs in alveolar epithelial cells [62]. Functional genetic variants in key cell cycle control genes, namely p21, p53 and cyclin D1, strongly modified the effect of air pollution on age-related lung function decline [63]. The same gene variants modified the association between oxidative stress-related factors and the risk of breast and colorectal cancer [64–65].

The expected benefit of genetics in chronic disease epidemiology

For clinical medicine and public health to benefit from the recent advances in various -omics disciplines, epidemiological research needs to be conducted in the context of internationally harmonised cohorts and biobanks. Very large sample sizes are needed for the investigation of complex gene-environment interactions and the identification of public health-relevant risk patterns. Projects such as the UK Biobank are characterised by the collection of many biological specimens, by the detailed lifestyle and exposure characterisation of subjects as well as by the identification of many different health outcomes, in many cases through linkage with disease and death registries [66]. Large biobanks and broad research consortia have led to the detection of numerous novel genes for age-related diseases through genome-wide association studies over the past few years [67].

However as only modifiable, exogenous risk factors can be the target for prevention, what then is the expected benefit from the tremendous investments into genetics over the past two decades? It is important to point out the differences between monogenetic and complex disorders in the context of this question. Our thinking about the benefits

of genetics has long been dominated by its link to monogenetic disorders. In genetic syndromes, the identification of disease causing DNA variants provides opportunities for diagnosis, reproductive counselling and sometimes drug development. The benefit of genetics in complex diseases is less obvious and more controversially discussed. The dramatic increase in age-related diseases over the past decades is primarily the result from changes in lifestyle and environment. Results from recent genome-wide association studies show that single gene variants are associated with age-related diseases mostly at relative risks below 1.50 [3]. Contrary to monogenetic disorders, genetic tests for age-related and complex diseases are of little to no value today on an individual basis. Rather, genetic and other biological markers in chronic disease epidemiology must be viewed as research instruments helping to improve our understanding of disease classification and susceptibility, biological mechanisms and causality in risk factor-disease associations [68].

The example of c-reactive protein (CRP) demonstrates some of the benefits of genetics. CRP is a correlate of low-grade chronic inflammation. Some evidence suggests that CRP may actively contribute to inflammation. However, as this evidence is inconclusive, it is still unclear whether the association between CRP and some age-related diseases including cancer is in fact causal [69]. The Mendelian randomisation approach benefits from the fact that inherited gene variants, contrary to blood concentrations, are stable over a person's lifetime and are neither influenced by disease nor by exogenous exposures. This approach was applied to explore CRP as a disease biomarker in several studies of different diseases. Mostly, CRP gene variants have been found to be associated with altered plasma CRP levels, but not with disease risks, suggesting that CRP may not have a causal role in the disease process.

In addition to the clarification of causality in exposure-disease associations, genetics also harbours the potential to improve understanding of susceptibilities. Few well characterised gene-environment interactions exist to date. Firstly, the effect of smoking on bladder cancer risk depends on the efficiency with which N-acetyltransferase 2 (NAT2) metabolises smoking carcinogens. The NAT2 efficiency is genetically determined [70]. Secondly, the effect of genetically inherited, severe alpha-1-antitrypsin deficiency on the development of COPD seems to be restricted to subjects exposed to inhaled toxicants, mostly from cigarette smoking [71]. Failure to consider genetic susceptibility may weaken the capacity to identify modifiable risk factors [3]. The reverse is true, too: failure to consider the lifestyle and environment of subjects may weaken the capacity to identify the most relevant disease genes in a specific population. The interaction of gene- and exogenous risk factor networks has been largely ignored in genome-wide association studies [72]. Yet, as statistical methods for assessing gene-environment interactions and considering *a priori* information for pathway analysis are now being developed [72–74], this will be an important next step in genetic epidemiology.

Conclusions

Obesity and air pollution are two globally important risk factors for age-related diseases and overall mortality. In both cases, the molecular and causal mechanisms mediating the adverse health effects remain poorly understood. As a result, causality of the disease associations of different obesity parameters and air pollution components is still a matter of debate. With regard to air pollution regulation, the identification of genetically and otherwise susceptible population groups is of great importance. The Swiss laws require legal limits for air pollutants to protect the most susceptible members of the population *(http://www.admin.ch/ch/e/rs/c814_01.html)*. It is hypothesised that alterations in systemic low-grade inflammation, insulin resistance and cell cycle control may, at least in part, underlie the adverse health effects of obesity and air pollution. Susceptibilities to these two exposures may thus, in part, be determined by variations in gene regulation of these signalling pathways. To test this hypothesis, interactions of obesity and air pollution with these selected gene variants must be investigated in future studies.

The public health relevance of understanding causal effects of obesity and air pollution, as well as common underlying mechanisms, is the fact that physical inactivity and excess calorie intake are tightly linked to air pollution, all indicators of urbanisation and globalisation of lifestyle [75]. The genetic background of different populations may further modify susceptibility to these risk factors. Asian populations seem to be more sensitive to obesity and exhibit higher risks for type 2 diabetes under comparable living conditions [76]. Finally, there is evidence that the age of exposure to western lifestyles modifies the impact of insulin resistance on chronic disease risk. Some studies suggest that malnutrition *in utero* or during early childhood is a predisposition to adult onset diabetes [77]. Thus, as mechanisms underlying ageing and chronic diseases are complex, research approaches must be complex, too.

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