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## Odd correlation: Parkinson's disease and melanoma. What is the possible link?

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### ABSTRACT

Parkinson's disease (PD) is a neurodegenerative disorder, characterised by depletion of dopamine in the striatum and loss of melanin-positive, dopaminergic neurons in the substantia nigra. Melanoma is a skin neoplasm arising from epidermal melanocytes. The epidemiology of melanoma focuses on well-known risk factors such as light skin and hair colour, gender, eye pigmentation, and ultraviolet (UV) exposure. Many studies have suggested an association between Parkinson's disease and melanoma. The mechanism underlying the possible connection between PD and melanoma is not clear and has aroused lots of interest. More interesting is that the link between these two diseases runs both ways. What is the underlying cause of this reciprocal association? Is it due to Parkinson's treatment? Is levodopa the reason for increased incidence of melanoma in people with the neurodegenerative condition? Are there any genetic, immune system irregularities or environmental risk factors that serve as the common denominator between these two conditions? Should we consider melanoma comorbidity with Parkinson's disease and *vice versa*? Some hypotheses include pigmentation changes in melanin and/or melanin synthesis enzyme like tyrosinase hydroxylase, autophagy deficits, disturbed form of metabolically controlled cell death, and changes of PD-related genes such as Parkin or  $\alpha$ -synuclein. Learning more about the relationship between PD and melanoma may lead to a better understanding of each disease and contribute to more effective treatments of both.

**Key words:** Parkinson's disease, melanoma, melanin, dopamine

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### Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease of the central nervous system (CNS), the second most frequent after Alzheimer's disease [1]. Its essence is the loss of substantia nigra in the brain, which is the area responsible for synthesis of dopamine, neurotransmitter necessary for proper functioning of the nervous system. Dopamine deficiency leads to neurotransmission disorders and the occurrence of typical symptoms, including: general slowness of movement, leaning forward, trembling hands (less commonly legs or headaches), problems with movement initiation, difficulty with standing up and performing everyday life activities such as washing, eating, or dressing [2]. The cause of the disease is not fully understood. It probably involves genetic and environmental factors, and the risk of developing the disease increases with age [3].

Epidemiological and toxicological studies emphasise the influence of environmental factors on the development of PD, and genetic studies show the role of specific gene mutations. Parkinson's disease affects up to 1% of the population over 60 years of age. It is a progressive disease that leads to increased dementia, mortality, and risk of death with decreased risk of cancer, except melanoma.

Only symptomatic treatment of PD is possible — it is aimed at improving the patient's quality of life and prolonging surviving for as long as possible in the best physical and mental form. Pharmacological treatment is introduced when the symptoms start to impact the patient's daily functioning. The therapy consists of simulating the function of dopamine as a transmitter (dopaminergic receptor agonists) or its supplementation (levodopa); however, it does not significantly increase patients' overall survival [4].

Melanoma is a malignant tumour from pigmented skin cells — melanocytes — that originate from neural

cells located in body integuments. Melanocytes produce an endogenous pigment melanin that protects the skin against the harmful carcinogenic effects of ultraviolet radiation. Melanocytes are found in the skin and additionally in the eye, mucosal epithelium, and the meninges. Skin melanomas are divided based on the melanocyte transformation site. They account for over 90% of all melanomas (3.7% of melanocytic tumours are localised in the eye, and 1.4% in the mucous membranes) [5]. In recent years, the incidence of melanoma has been constantly increasing worldwide. The annual increase in incidence of this cancer is about 3–7% [6]. The peak of incidence is, on average, at 52 years of age. In Poland, the number of melanoma cases in the last thirty years has increased threefold. Annually over 3000 new cases are found and 1500 people die from this disease [7].

The main risk factors include genetic factors, a fair phototype of the skin, excessive exposure to ultraviolet radiation from solar and artificial radiation, sunburn at an early age, and individual predispositions [6]. Early identification of the primary tumour (excision biopsy of primary lesion) and potential metastases to regional lymph nodes (sentinel lymph node biopsy) give a unique opportunity to cure patients with non-advanced skin melanoma, evaluated in Breslow metric scale in terms of depth of dermis infiltration below 1 mm. In about 80% of patients, melanoma is a localized lesion at diagnosis, 15% of patients present with regionally advanced stage, and in 5% of patients have the disease in disseminated stage at presentation [7].

Parkinson's disease is diagnosed with a frequency of 10–50 people per 100,000 population per year. The disease occurs in 100–300 people per 100,000 individuals in the population [1]. This frequency increases with age, especially after 60 years of age. The relationship between PD and melanoma was noticed about half a century ago. The first suspicions concerned the drug levodopa, which was used to treat PD [8]. Subsequent observations did not confirm this relationship because the increased incidence of PD in people with melanoma is unrelated to dopaminergic therapy [9]. Many publications in prestigious journals and meta-analyses confirm the existing relationship between PD and melanoma, and emphasise not only the role of genetic and immunological factors, but also the common origin of embryonic melanocytes and neurons [10, 11]. Although the correlations themselves seem to be confirmed, new hypotheses are still being proposed in an effort to explain them. The aim of this article is to review the most interesting hypotheses.

Numerous epidemiological studies and meta-analyses support the relationship between PD and melanoma [10, 11]. The researchers also point out that this link is bi-directional and that melanoma also increases the risk of PD. Recent reports based on large samples have

shown that people with PD are four times more likely to develop melanoma, in contrast to other malignancies of internal organs related to, for example, smoking [12]. Also, in people with melanoma, there is a four-fold greater risk of developing PD [10]. The reasons for this interaction remain unexplained.

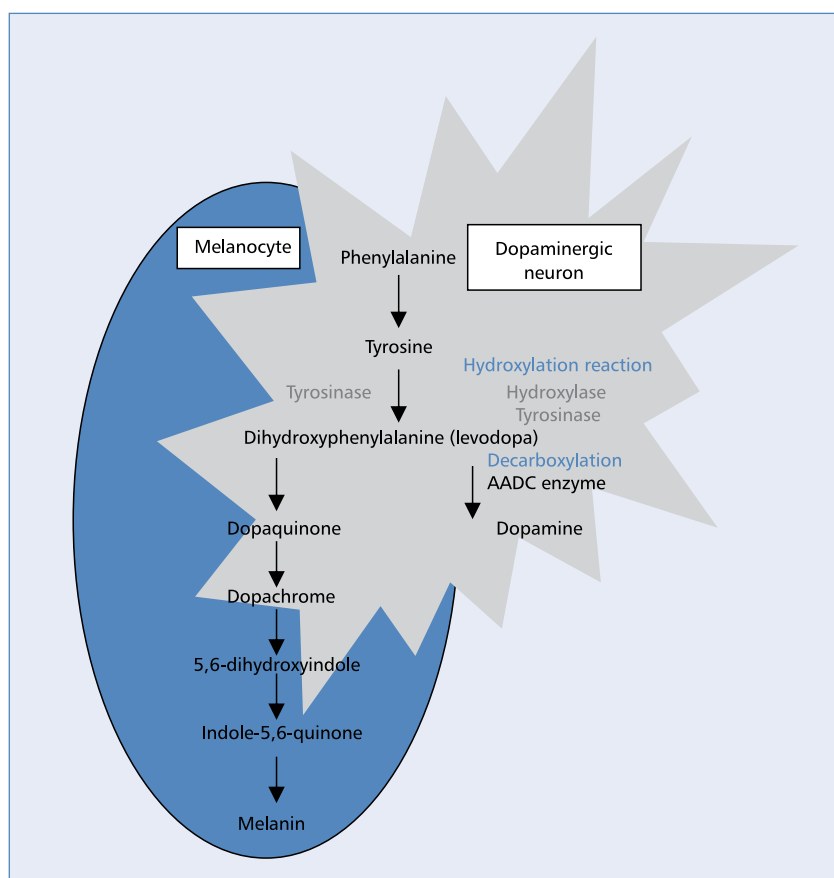
## Pathogenesis of Parkinson's disease

The essence of the disease is the irreversible progressive loss of dopamine-producing neurons containing neuromelanin in the substantia nigra (hence the name) with the presence of eosinophilic protein inclusions, termed Lewy bodies (LBs), in their cytoplasm [3]. Lewy bodies result from accumulation of aggregated form of  $\alpha$ -synuclein ( $\alpha$ -Syn) protein. The loss and degeneration of dopaminergic neurons translates into a significant deficiency of dopaminergic transmission and associated neurological disorders (motor and mental retardation, resting tremor, muscle stiffness). Intravital diagnosis of Parkinson's disease is based on clinical symptoms and neurological differential diagnosis, which in the early stages of disease is difficult and in the advanced phase does not translate into any therapeutic benefits [4]. Degeneration and loss of dopaminergic neurons is a progressive process, with no effective treatment so far.

The following are considered as the main factors involved in neurons damage:

- oxidative stress, because it intensifies the enzymatic and non-enzymatic oxidation of dopamine;
- mutations of genes from the *PARK* family;
- abnormal deposition and aggregation of cytoplasmic proteins, especially  $\alpha$ -Syn that accumulates in the form of Lewy bodies;
- mitochondrial dysfunction;
- apoptosis disturbances;
- improper autophagy process;
- mechanism of cell death through ferroptosis.

Physiological production of dopamine involves the formation of numerous intermediates that are highly reactive and generate oxidative stress in neurons (Figure 1) [13]. Dopamine itself does not accumulate in the cytosol of dopaminergic neurons and is protected in synaptic vesicles VMAT-2 because it is a highly reactive compound that damages the cytoplasmic and mitochondrial proteins of the dopaminergic neuron. Parkinson's disease occurs in older age, perhaps due to the depletion of mechanisms that counteract reactive oxygen. Post-mortem brain examinations of patients with PD show signs of damage to dopaminergic neurons due to oxidative stress [1, 3]. Clinical and experimental studies also indicate the effect of oxidative stress associated with gene mutations:  $\alpha$ -Syn or parkin [13].



**Figure 1.** Steps of melanin and dopamine synthesis (in simplified form). Dopaminergic neurons use both dopamine and neuromelanin synthesis pathways, whereas melanocytes utilise a synthetic pathway directed exclusively to melanin. AADC — amino acid decarboxylase

The aetiopathogenesis of PD also highlights the shortage of physiological antioxidants and free radical scavengers, as demonstrated for uric acid [4].

### Melanin and neuromelanin

Melanin is the main determinant of skin and hair colour in humans, and its type and quantity determine the skin phototype [14]. Melanin exists in neurons in the substantia nigra and is called neuromelanin. It is a protective factor for neurons against oxidative stress during neurotransmitter production, i.e. dopamine [13]. Melanin disorders in the skin can lead to development of various skin cancers, including melanoma, while Parkinson's disease correlates with neuromelanin abnormalities, suggesting that this pigment is a key link between both diseases [13, 14].

Melanin in the epidermis protects melanocytes and adhering keratinocytes from the harmful effects of UV radiation on cellular DNA, but in the case of transformed melanocytes its increased expression inversely correlates with overall survival and disease-free survival

in patients with advanced melanoma (grade III and IV), accelerating tumour progression [14]. In light of new research, the photoprotective role of melanin is not as unambiguous as it was previously thought. It transpires that melanin under the influence of accumulated energy from UVA radiation secondarily damages melanocyte DNA under oxidative stress conditions and paradoxically promotes carcinogenesis of these cells after cessation of the sun's action [15]. During the so-called dark phase, after cessation of UVA action on the skin, energetically excited and oxidised melanin passes from melanosomes, in the form of monomers, to the cell nucleus and induces the formation of pyrimidine dimers of cytosine, damaging the double helix of DNA [16]. DNA damage is greater in the presence of oxygen radicals also formed under UVA influence [17]. Moreover, sunlight affected reddish yellow melanin, e.g. pheomelanin, generates — by its synthesis — the formation of reactive oxygen species (ROS), which increase their harmful effect on DNA, proteins, and cell organelles. The harmful effect of UVA on melanocyte DNA is therefore increased by melanin and ROS during solar exposure and sustained afterwards despite sun exposure cessation. Inhibition of

melanin synthesis and the use of free radical scavengers as well as nitric oxide synthase (NOS) and NADPH oxidase (NOX) inhibitors prevents the formation of pyrimidine dimers of the DNA strand [15]. In summary, melanin, in particular reddish yellow pheomelanin, does not effectively protect against the sun, but promotes DNA mutations and carcinogenesis the more the skin is exposed to UVA radiation in combination with free oxygen radicals [16]. The results of these experimental studies explain the epidemiological data that fair phototypes have an increased risk of melanoma after sunburn in their clinical history [18].

A strong electron stimulation of melanin occurring under the influence of UV and free oxygen radicals, called chemiexcitation, was first found in mammals and just in melanocytes. It is analogous to the chemical reaction used by fireflies in the production of light [19]. Chemical excitation of melanin by reactive electrons generates a new important source of genome instability and theoretically can occur everywhere where melanin exists and ROS are generated. This theory, by analogy, does not exclude dopaminergic neurons producing neuromelanin and generating large amounts of reactive oxygen species in the substantia nigra from similar pathogenic phenomena. However, this is just speculation and there is no such research in PD, although oxidative stress is mentioned as the main factor responsible for the irreversible damage and loss of dopaminergic neurons [4].

Neuromelanin also has a dual role. On one hand, it protects dopaminergic cells against oxidative stress, and on the other hand, it damages them in PD, as has been shown by numerous studies [13]. Neuromelanin, like melanin, is a pigment with two faces. With age, its amount is accumulated in cytosol of dopaminergic neurons, and in the embryonic period and at birth it is practically absent. Perhaps the expression of neuromelanin is regulated by factors related to maturation of these cells, dopamine itself and environmental factors influence, as it is in skin melanocytes. Under physiological conditions neuromelanin protects neurons from harmful effects of dopamine and its oxidised derivatives. It converts quinones and semiquinones, which are formed in the dopamine synthesis process and are potentially toxic to cells, into stable and non-reactive polymers. Quinones modify the structure of cytoplasmic proteins and are involved in the formation of insoluble filamentous aggregates similar to  $\alpha$ -Syn. Another harmful effect of quinones is inhibition of NADPH reductase in the mitochondria, which increases oxidative stress. These effects are counteracted by neuromelanin. The pigment also binds with high affinity and sequesters heavy metals, which have a proven neurodegenerative effect, such as iron, copper, zinc, lead, or aluminium. Iron associated with neuromelanin inhibits chemical reactions in which ROS are generated.

Under favourable circumstances, however, neuromelanin can become toxic to dopaminergic neurons. This happens in cases of heavy metal poisoning, when its ability to sequester metal ions is depleted. The iron-saturated neuromelanin paradoxically oxidises dopamine and transforms it into harmful and highly reactive derivatives damaging protein structures in neurons. What is more, it supports reactions generating free radicals. Neuromelanin released from damaged neurons induces and inflammation in the substantia nigra in the substantia nigra by microglial cells activation. Heavy metals released from the neuromelanin, additionally damage *de novo* the neuronal cells. Microglial cells with phagocytic properties being activated by neuromelanin presence start to produce neurotoxic inflammatory mediators, i.e. tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-6 (IL-6), and nitric oxide, which together with free oxygen radicals sustain and intensify destructive processes in the substantia nigra.

There is no doubt the role of neuromelanin is very complex, and its final effect depends on the influence of environmental factors, dopaminergic, mitochondrial, and inflammatory processes generated by microglial cells, and translates into oxidative reactions, playing a role in the pathogenesis of PD [13]. It cannot be ruled out that the electron flow from highly reactive oxygen species and neuromelanin oxidation also occurs in the substantia nigra similarly as it is in the skin, under the influence of impaired dopamine synthesis pathways or deficiencies of natural antioxidants, as demonstrated by a current meta-analysis on decreased concentration of uric acid in PD [4].

Also, changes in activity of enzymes involved in the synthesis of melanin and neuromelanin, such as tyrosinase and tyrosine hydroxylase (Figure 1), respectively, play an important role in altered susceptibility to melanoma and PD. The tyrosine hydroxylase catalyses in the presence of oxygen the hydroxylation of tyrosine to dihydroxyphenylalanine, from which the neurotransmitter dopamine or neuromelanin is formed in the substantia nigra [20]. In melanocytes, tyrosinase catalyses the formation of dark eumelanin and reddish yellow pheomelanin. In the course of these reactions, dopaquinones and other free radicals are formed, which have potential toxic effects on cells. In fact, in substantia nigra they lead to neuronal damage, while in the skin they damage the genetic material, increasing the risk of carcinogenesis [21].

### Drugs used in Parkinson's disease and melanoma

The synthesis of dopamine and melanin occurs in the common pathway (Figure 1), in which levodopa is a substrate for enzymes and melanin synthesis, which is why it was suspected that levodopa increases the incidence of

melanoma [22, 23]. The probable relationship between levodopa and the development of melanoma was first described in 1972 [8]. Opponents of this theory argue, however, that exogenous L-dopa is not possible to be utilized by melanocytes and moreover toxicity of L-dopa against melanocytes has been demonstrated *in vitro* [24]. Subsequent randomised, prospective studies have also not confirmed this hypothesis. This theory is strongly supported by the fact that the increased incidence of melanoma occurred prior to the diagnosis of Parkinson's disease and levodopa introduction [9, 12]. There is also information in the literature about increased incidence of non-melanoma (a standardised SIR risk index of 1.95) skin cancers in people with PD, with an SIR index of 1.37 for basal cell carcinoma and 1.15 for squamous cell carcinoma, in a Danish patients registry, which also excludes levodopa as the cause that links both diseases [12, 25, 26]. Other cancers in patients with PD, apart from the most common melanoma, include breast and prostate cancers [9, 26, 27]. Unrelated to the treatment of PD and confirming the genetic basis of both diseases is the fact that these diseases are also diagnosed in close family members [27].

Other agents used to treat Parkinson's disease, such as selegiline and CEP-1347, also have no effect on the relationship between PD and melanoma [28].

### Genetic basis of Parkinson's disease and melanoma

There are population based studies indicating the risk of PD increases with fair colour of hair. An interesting hypothesis is the linking of the gene polymorphism determining red hair colour as an explanation of the correlation of both diseases, namely variant *R151C* of melanocortin 1 receptor gene (*MC1R*), which accounts for a fair skin phenotype with reduced UV protection, contributing to an increased risk of melanoma development with a simultaneously increased incidence of PD [29]. In this variant, arginine at position 151 is replaced with cysteine, and in the case of homozygote of the *R151C*, Cys/Cys allele, only melanin conditioning the red hair colour is formed [29]. This melanin, called pheomelanin, plays the key pro-oxidative role as a final product of the *MC1R* gene.

*MC1R* is present on nerve cells in the brain and is thought to play a neuroprotective role, depending on the genetic variant in which it occurs. A similar relationship was found in the Spanish population for the *R160WMC1R* variant, but subsequent studies did not confirm the significance of this variant in the genetic background of PD [29].

Neuromelanin, in addition to reddish yellow (pheomelanin) and black (eumelanin), is the third type of human melanin synthesised in dopaminergic neurons of the substantia nigra. In fact, it is a combination

of these two types in the right proportions; its core is pheomelanin, covered on the surface by eumelanin. In red-haired people, the thinning or even lack of eumelanin in neuromelanin may determine the sensitivity of dopaminergic neurons to neurodegenerative processes associated with oxidative reactions or sensitivity to dopaminergic toxins, i.e. 6-OHDA or MPTP [30].

Interestingly, skin cells collected from red-haired patients show gene defects reported in neurodegenerative disorders, i.e. Parkinson's disease, Alzheimer's disease, and Huntington's disease [31], which indirectly links the reddish yellow melanin phenotype with neurodegenerative processes. Interestingly, *in vivo* imaging studies show a relationship between the fair skin phenotype and increased echogenicity of substantia nigra in the brain.

In the substantia nigra neurons in mice, the expression of *MC1R* is localised in the cytoplasm and overlaps the expression of tyrosine hydroxylase involved in dopamine synthesis, which may indicate their functional association [30]. And it seems to be so because the mouse model has shown that the "red-haired" variant of the *MC1R* gene reduces the production of dopamine in the substantia nigra and increases the sensitivity of brain cells to harmful dopaminergic substances. The phenotype of the "red-haired" variant of the *MC1R* gene associated with decreased dopamine production is more evident with mice aging, which also confirms the age factor in PD in humans [1].

This study is the first to show the direct impact of the red-haired variant of the *MC1R* gene associated with melanoma on the survival of dopaminergic neurons in the brain and may provide evidence for targeting *MC1R* as a new therapeutic strategy for PD [29, 30]. At present, the efficacy of *MC1R* agonists in acute phototoxic reactions, depigmentation diseases and erythropoietic protoporphyria is being assessed in clinical trials. Perhaps the use of such strategy in PD will prevent the neurodegeneration processes associated with the inactive homozygous "red-haired" *MC1R* allele.

Other genes that are considered in the aetiopathogenesis of both diseases include mutated *PARK2* [32, 33],  $\alpha$ -synuclein (*SNCA*) [34, 35], *DJ-1* [36, 37], or *LRRK2*, which is a homologous equivalent to mutated BRAF kinase in melanoma cells [27, 30].

The autosomal recessive germinally mutated *PARK2* gene determines PD at an early age. The gene is located in the fragile part of chromosome 6, in *locus* 6q25-q27, where other numerous tumour suppressor genes are located, that are susceptible to easy deletion, which promotes the development of tumours, especially of the breast and ovary [32]. Mutations of *PARK2* gene encoding ubiquitin E3 ligase, which belongs to tumour suppressor genes, are found in neurons of the juvenile genetic variant of Parkinson's disease, glioblastoma multiforme, as well as colon and lung cancer [33]. The loss of *PARK2* heterozygosity was also found in melanoma cells [27].

Another common gene for PD and melanoma is *SNCA* coding for  $\alpha$ -synuclein. Its mutated forms promote disturbed degradation and accumulation of filamentous aggregates in Lewy bodies [34] and the development of neurodegenerative diseases leading to dementia. Overexpression of  $\alpha$ -synuclein inhibits the phosphorylation of both enzymes involved in the synthesis of dopamine, tyrosine hydroxylase, and L-dopa amino acid decarboxylase (AADC) converting L-dopa into dopamine, which inhibits the synthesis of the neurotransmitter (Figure 1).

Melanocytes also contain  $\alpha$ -Syn, which is regulated by a transcription factor, a product of *MITF* (microphthalmia-associated transcription factor) gene. *MITF* regulates the expression of genes required for melanin synthesis, i.e. tyrosinase and tyrosinase-like proteins, and *MITF* mutation leads to melanocyte transformation and melanoma development. In the primary and metastatic melanoma, significantly increased expression of  $\alpha$ -Syn protein is observed [35]. Currently, we cannot explain the role of  $\alpha$ -Syn in cutaneous melanocytes and melanoma pathogenesis.

*DJ-1* is a highly conservative common gene. Similarly to the *PARK2* gene, its mutations were found in a genetically conditioned, autosomal recessive type of PD manifesting at an early age and sporadic variant. It was originally called *PARK7* [36]. *DJ-1* plays an important role in the regulation of oxidative stress and is located in cytoplasm, cell nucleus, and in the mitochondria. Loss of its function promotes damage to substantia nigra neurons as a result to oxidative stress, and its concentration increases in cerebrospinal fluid (CSF) in patients with advanced PD. Increased levels of circulating *DJ-1* are also found in patients with melanoma [37].

Another interesting issue is the observation that patients with melanoma without concomitant Parkinson's disease have a 10 times greater risk of death due to metastatic melanoma compared to patients with melanoma co-existing with PD [10]. It suggests that PD pathomechanism can inhibit melanoma progression and the ability to create metastases. Perhaps an abnormal activation of the innate and adaptive immunity in PD, responsible for inflammatory neurodegenerative processes may indirectly inhibit the activity of transformed melanocytes in the progression of melanoma.

### Autophagy deficit

Interesting theories include the deficit of autophagy or "cellular recycling mechanism". Autophagy disorders lead to accumulation of damaged organelles and deposition of pathogenic protein aggregates in Lewy bodies, which has a proven relationship with neurodegenerative diseases leading to dementia [38, 39]. The clearance of

neuronal  $\alpha$ -Syn in PD is impaired for two reasons:  $\alpha$ -Syn mutation and its resistance to the catabolic effects of autophagy, and impaired autophagy associated with the deficit of regulating chaperone proteins (hsc70) and lysosomal LAMP2A. Under physiological conditions, the half-life of  $\alpha$ -Syn is 46.5 hours. In PD, its accumulation and pathological aggregation is observed, which promotes the degeneration of dopaminergic neurons [38].

In neoplastic transformation, there is a disturbed presentation of antigens, a decrease in autophagy, and thus the escape of the tumour from immune surveillance [40, 41]. The reduced *DJ-1* regulated autophagy capacity was found in prostate, breast, and lung cancer cells in which the expression of the DJ-1 protein is high. So the mutant form of *DJ-1* (*PARK7*) described in the pathogenesis of PD promotes tumour formation and inhibits the activity of p53 anti-oncogene [40].

### Smoking in melanoma and Parkinson's disease

Many publications showed an inverse relationship between the incidence of melanoma and smoking, as well as for Parkinson's disease [1]. After considering other factors in control studies (age, sex, race, skin type, and history of sunburn) former smokers have a 60% lower risk of melanoma in comparison to non-smokers, and in current smokers the risk is reduced by 35% [42]. A similar inverse relationship exists between smoking and PD, which is explained by the protective effect of smoking on dopaminergic neurons and the antioxidant properties of nicotine [1, 12]. Nicotine and hydroquinone found in cigarette smoke have also been shown to inhibit  $\alpha$ -Syn aggregation, which plays a role in the aetiopathogenesis of PD and dementia.

### Olfactory (odorant) receptors

Interesting new cognitive abilities in the aetiopathogenesis of melanoma and PD offer olfactory/odorant receptors (OR) present on pigmented skin cells and the dopaminergic nerves [43]. The olfactory receptors regulate melanogenesis in melanocytes and neurons of the substantia nigra. They are the largest family of all known receptors in vertebrates, with over 391 types described in humans. In PD their expression is reduced, which may favour neurodegenerative processes.

There are interesting hypotheses supported by experimental data that olfactory receptor agonists, which include specific chemical and fragrance substances, may have a beneficial effect on the disturbed functioning of melanocytes and dopaminergic neurons in melanoma and PD [44]. In melanoma increased OR51E2 recep-

tor expression was observed, and its stimulation with a specific ligand inhibited the proliferation and migration of melanoma cells, while inducing apoptosis in them [45]. The authors of the abovementioned study suggest that the family of olfactory receptors may offer an interesting and easily available topical therapeutic intervention in melanoma, as well as a preventive one via nasal airway in PD.

### Disorders of ferroptotic programmed cell death

Another interesting phenomenon combining melanoma with degenerative brain diseases, including PD, is recently identified ferroptosis [46]. It is programmed cell death that is morphologically, biochemically, and genetically different from apoptosis, necrosis, and autophagy. While the physiological role of ferroptosis is not explained, its aetiology results from the imbalance of iron-regulated oxidation processes leading to lipid peroxidation toxic to the cell and disturbed metabolic processes [47]. Cells in which oxidation processes are constantly taking place and ROS are activated, are susceptible to ferroptosis, such as melanocytes and neurons of the substantia nigra due to the synthesis of melanin and dopamine. Ferroptosis is induced by inhibition of cysteine uptake that reduces intracellular glutathione levels (GSH) and the antioxidant status of cells [48].

An important aspect from the oncological point of view seems to be the fact that non-apoptotic forms of cell death may facilitate the selective elimination of specific cancer cells. Recently, it has been reported that resistant mesenchymal tumours depend on the GPX4/lipid peroxidase pathway, which allows ferroptosis to be avoided [49]. This observation gives an importance to ferroptosis in the new strategy of anticancer drugs [50]. In addition, drugs that induce a suicidal cell death process through ferroptosis may be used to treat de-differentiated melanoma cells that have lost the ability to die in this mechanism. Further studies in patients with grade IV melanoma are warranted if the induction of impaired ferroptosis improves the efficacy of immunotherapy and anti-BRAF targeted therapy [51].

Ferroptosis is also involved in neurodegenerative diseases because it has been shown that ferrostatin and iron chelators are effective in the Parkinson's disease model [52]. Recent evidence suggests that iron is an interesting therapeutic target for PD. Application of the iron chelator, i.e. deferiprone in neural cell cultures and mouse model, reduces oxidative stress and increases the availability of dopamine, which consequently improves the existing motor disorders and prevents their deterioration [53].

The issue of using ferroptosis in the treatment of melanoma or neurodegenerative disease creates in-

teresting and new possibilities for further research of another phenomenon that links transformed melanocytes with degenerating neurons in the substantia nigra of the brain.

### Summary

We do not know the exact correlation between Parkinson's disease and melanoma, or it is so complicated that we do not fully understand it. Undoubtedly, both diseases relate to dendritic cells with the same embryonic origin, melanocytes producing melanin and neurons producing dopamine and neuromelanin. Although these cells differ in localisation and function, they have common embryo-determined genetic material, as confirmed by numerous studies on similar gene expression and mutations [1, 3].

It is known now, that melanin itself plays an important role in the malignant transformation of melanocytes in addition to UV radiation, especially its reddish yellow variety with free oxygen radicals [16]. It could be similar in the case of neuromelanin, which under certain conditions intensifies oxidation processes, inhibits reducing reactions, damages dopaminergic neurons, and generates inflammation induced by phagocytic cells of microglia [13]. Current knowledge shows that the development of both diseases is influenced by complex genetic background, environmental factors, and oxidative stress [27], which is also confirmed by the last study investigating the role of melanocortin 1 receptor gene (*MC1R*) in the "red-haired" variant in substantia nigra in mice [29]. The genetic basis of both diseases is presented extensively in the review paper by Inzelberg et al. [54] and summarised in Table 1.

More information on the relationship between Parkinson's disease and melanoma may lead to a better understanding of these diseases and provide a basis for further research, as in the case of ferroptosis [51]. Such studies may influence the findings of new therapeutic strategies and molecular targeted therapies, thus contributing to more effective treatment of both diseases in the future. There are currently some indications that the use of antioxidants and free radical scavengers may have a neuroprotective effect and protect against the development of melanoma, but only theoretically, because supporting clinical trials do not exist [4, 15].

It is also worth considering the introduction of screening tests for the early detection of melanoma in patients with nervous system diseases. There are currently no guidelines for recommending regular screening of patients with PD towards melanoma and vice versa. It is worth emphasising the need to raise awareness about the ongoing correlation among doctors, patients, and their families [9]. Unfortunately, PD cannot be

**Table 1. Abnormal genes and disorders found in dopaminergic pigmented cells of the nervous system in Parkinson's disease (PD) and melanocytes in melanoma (MM)**

Gen/gene product/ /phenomenon	Parkinson's disease	Melanoma
<i>SNCA</i> /α-synuclein	Mutation in AD variation of PD α-synuclein aggregates in Lewy bodies Overexpression inhibits the synthesis of dopamine	α-synuclein present in MM and nevi
Parkin	Mutation in AR variation of PD and sporadic PD	Expression in MM
<i>PARK2</i> /ubiquitin ligase E3	Mutation in AR variation of PD	Loss of heterozygosity of <i>PARK2</i> in MM
<i>DJ-1</i> ( <i>PARK7</i> )	Mutation in AR variation of PD and sporadic PD	Inhibits apoptosis and autophagy phenomena in MM Increased serum concentration in MM patients
LRRK2	Mutation in AD variation of PD	Mutated <i>BRAF</i> in MM is an analogue
<i>MC1R</i> /melanocortin receptor 1	Red hair, a fair phenotype associated with an increased risk of PD The dark variant has a neuroprotective effect	"Fair skin" variant increases MM risk
Variant <i>R151C MC1R</i>	PD risk increase No or trace amount of eumelanin in neuromelanin	Hyperactivation of pheomelanin under the influence of UVA and ROS damages DNA of melanocytes
Odorant receptors (OR)	Decreased expression in PD	Increased OR51E2 expression in MM Regulation of proliferation, migration and apoptosis in MM
Ferroptosis (metabolic programmed cell death)	Increased ferroptosis	Resistance to ferroptosis
MITF	Regulates the activity of enzymes in dopamine synthesis	Mutation in MM
The effect of nicotine	Smoking correlates inversely with PD risk	Smoking correlates inversely with MM risk

AD — autosomal dominant; AR — autosomal recessive

prevented or cured effectively [4]. Early diagnosis based on clinical examination and neurological experience is difficult and imperfect in PD. Melanoma, on the other hand, is a cancer that is virtually completely cured when it is detected early enough [7]. Nevertheless, it is still recognised too late. In Poland, unfortunately, the mortality rate due to melanoma according to the National Cancer Registry is 20% higher than the average for the European Union; therefore, all activities that increase vigilance towards this cancer are justified.

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