A stem-cell ageing hypothesis on the origin of Parkinson's disease

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A transcriptome-wide blood expression dataset of Parkinson's disease (PD) patients and controls was analyzed under the hypothesis-rich mathematical framework. The analysis pointed towards differential expression in blood cells in many of the processes known or predicted to be disrupted in PD. We suggest that circulating blood cells in PD patients can be in a full-blown PD-expression state. We put forward the hypothesis that sporadic PD can originate as a case of hematopoietic stem cell/differentiation process expression program defect and suggest this research direction deserves further investigation.

Parkinson's disease (PD) is the second most common neurodegenerative disorder, after Alzheimer's disease (1). The majority of PD cases are sporadic, with only 5-10% of cases presumed to have a well-defined singular genetic cause. Although the etiology and progression mechanisms in sporadic PD are not yet settled, there has been a diversity of significant insights and hypothesis proposed in recent years (1).

We performed a hypothesis-rich mathematical analysis (Supp. Mat.) (2) of landmark genome-wide expression data on RNA extracted from whole blood of 50 predominantly early-stage PD patients (mean Hoehn and Yahr stage 2.3, range 1-4) and 55 age-matched controls (3). This novel hypothesis-rich framework is a mathematical framework ideal for addressing systems biology problems where there is potential to jointly leverage a diversity of existing biological knowledge and quantitative data on a large number of variables. Most interestingly, the analysis hints at differential expression in blood cells in many of the processes known or predicted to characterize PD in neurological tissues (Supp. Mat.). This opens the possibility that, more than just exhibiting side-effects of the presence of PD in neuronal tissues, circulating blood cells in PD patients may be, at least expression-wise, in a full state of PD, much in the same way as affected neurons are.

Taking this observation as a starting point, we put forward an alternative hypothesis on the nature and etiology of sporadic PD (the word sporadic will be subsumed henceforth) (Fig.1). We first suggest that, at its root, PD is best defined as a characteristic deviation from normality in the expression program of cells. We call it the PD-expression state, or PD-state for short. Thus, we propose that circulating blood cells in PD patients are in a full PD-state. The PD-state would therefore be a generic cell state, not specific to neuronal cells. However, as also argued by others (4), due to the particular critical role that some expression programs play in neuronal tissues, the PD-state is catastrophic in them, leading to the observed neuronal-associated pathology. A crucial question then becomes whether the PD-state is propagated from neuronal cells to blood cells, or vice-versa. That is, where does it originate? Recent studies show PD pathological signs, such as Lewy bodies and Lewy neurites, being propagated to healthy neuronal grafts in PD patients only over a time-scale on the order of a decade (5; 6). Considering, by comparison, the much shorter life-time of most blood cells (the lifespan of red blood cells and platelets is 127 (7) and 4.4 (8) days, respectively), we argue that it is comparatively more realistic that the PD-state originated in the blood cells.

PD is markedly age associated, with only 4% of PD cases diagnosed in the United States occurring before age 50 (9). There is evidence that hematopoietic stem cells (HSCs) age, showing an altered cell surface phenotype and changes in metabolic activity and gene expression (10; 11). Recent studies demonstrated that this ageing process is a consequence of accumulation of DNA damage (12). These lesions can be propagated to daughter stem cells and to downstream lineages through the processes of self-renewal and differentiation. We propose that the PD-state acquired by blood cells could be a case of hematopoietic stem cell ageing. Under this premise, circulating endothelial progenitor cells, which undergo endothelial cell differentiation under appropriate inductive signals and form neovessels (13), become a candidate vehicle for propagation of the PD-state to other cells in the human body.

An early sign of PD is impaired sense of smell (14). The olfactory bulb was recently reported as being a site of continuous stem cell based tissue regeneration (15). Gastrointestinal dysfunction is another early sign of PD reported as much as 10 years before motor symptoms appear (16). Gastrointestinal function is very sensitive to the proper function of intestinal epithelial cells (17), which are replenished by local adult stem cells with tissue turnover in under 7 days (18). Assuming the ability of HSCs to propagate the PD-state to adult stem cells via circulating progenitor cells, would explain the early PD symptoms in sites of very active stem cell based tissue regeneration. The initial propagation of the PD-state to these tissues could be due to rapid self-renewing and stem cell plasticity facilitating stem cell reprogramming by the endothelial cells derived from the circulating progenitor cells (19; 20). Of note, α-synuclein has been shown to be expressed in endothelial cells (21). Alternatively, the niche stem cells might be directly under replenishment by transformed endothelial cells (22).

Our proposition is that the PD-state is initially disseminated in a shorter time-frame through the differentiation process of active stem cell niches. Then, over a distinct slow time-scale on the order of years, the PD-state propagates through stable tissues (19).

We believe that the hypothesis presented here deserves further investigation and that some experiments should be performed to validate this line of research. To confirm the involvement of circulating progenitor cells in the propagation of PD-state, $CD34^+$ cells (or subpopulations of $CD34^+$ cells) (23) collected from the peripheral blood of PD patients should be characterized at gene level and the "genetic fingerprint" compared to the one observed for PD-state neurons. To evaluate whether PD originates at the bone marrow and propagates to the nervous system, or rather initiates at the gastrointestinal tissue, propagates to the nervous system and only via this latter one, reaches the bone marrow, we suggest a long-term, large-scale study where the blood of individuals with ages above 50 years but without PD symptoms would be collected and analyzed over 10 years. If the bone marrow is implicated in the origin of PD, circulating progenitor cells will exhibit a PD-state profile before motor symptoms appear. In contrast, if motor symptoms appear before the PD-state profile is observed in circulating progenitor cells, then the bone marrow is not the origin but rather yet another late stop in the progression of the disease. We chose to highlight one particular hypothetical path from stem-cell ageing to PD, but variant paths cannot be excluded at present. For instance, PD could also originate in the transformation (ageing) of intestinal epithelial stem cells ($Lgr5^+$ cells). Of note, these stem cells have been recently identified as the origin of intestinal cancer (24). In this regard, the additional collection and characterization of intestinal biopsies from the individuals in the aforementioned proposed study would be pertinent to discriminate between these alternate possibilities.

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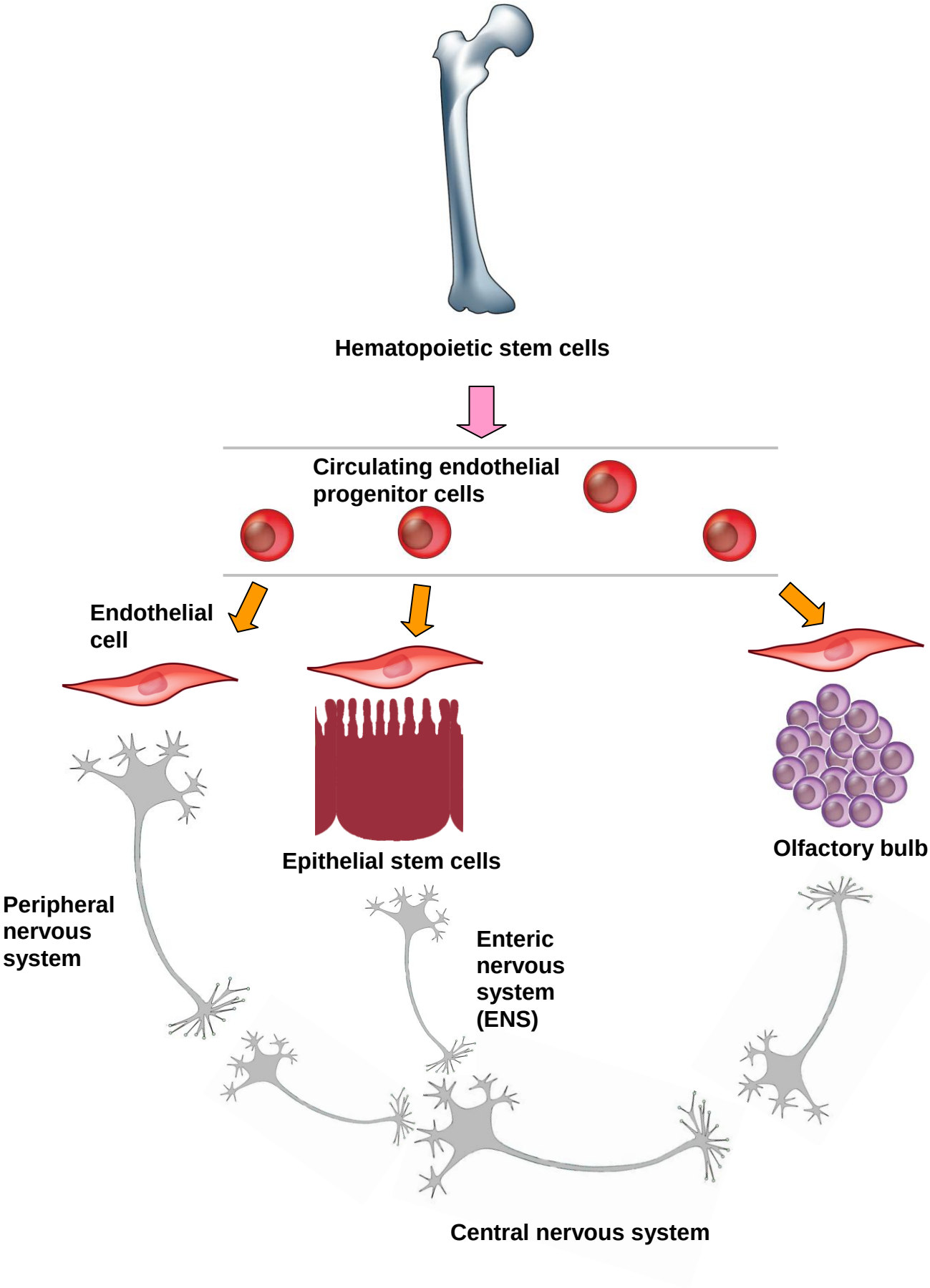

Figure 1 - Bone marrow-derived stem cells as the origin of PD. According to this hypothesis, the PD-state originally appears in bone marrow-derived stem cells due to ageing. Bone marrow-resident hematopoietic stem cells give rise to blood cells in a PD-state, including circulating endothelial progenitor cells (CEPCs). CEPCs differentiate into endothelial cells which are incorporated into blood vessels. These vessels then propagate the disease at different sites of the human body. The first symptoms of the disease (as early as 10 years before motor symptoms) would occur at places where the cell turnover is high, for instance at gastrointestinal tissue and at the olfactory bulb.