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Revisiting Melanin Metabolism with Revision

Revision of Our Research on Grey Hair Turning Black with Bioinformatics

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Genesis of this report is due to several requests, initially generated by publication in a regional news magazine, Gujarat Medical Journal. We noted, as an accidental finding in our ongoing research on neuro-degenerative diseases treated with Bone Marrow derived Mesenchymal Stem Cells (BM-MSCs) or with Adipose Derived Mesenchymal Stem Cells (ADMSCs). We decided to academically progress the research by publishing it in a journal devoted to stem cell research [1]. This publication in turn has generated global interest and we are receiving reprint requests and the protocols. Meanwhile we have successfully translated ADMSCs to all three germinal layers [2]. Potential is thus expanded to a new drug discovery [3] OA paper [4] Diabetes paper.

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REVISITINGMELANINMETABOLISMWITHREVISION

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Revision of Our Research on Grey Hair Turning Black with Bioinformatics

Bhaskar Vyas [α], Rajni Vyas [σ] & Anant Marathe [ρ]

I. Introduction

Bioinformatics is a science. It is used to analyze and interpret the biological data with interdisciplinary inputs. It is performed in a computer, i.e. in a dry lab to analyze biological queries that are answered in a progression mode that may go on indefinitely till homeostasis is reached.

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Advances in bioinformatics have so progressed that using computers as a dry lab, enormous data can be accessed. We therefore report on the progression of our research on MSCs as well as results obtainable with bioinformatics on several cytokines that may have impinged our research.

II. Materials and Methods

BM-MSCs are reported to have 120 cytokines and chemokines.[5] To publish the data on all 120 molecules that are being secreted from BM-MSCs would be far too voluminous. So, we summarize only with a largely secreted molecule, IL-6. IL-6 has a property to impact the functions of the cells of various tissue types. IL-6 search yields two different leads.

1-Molecular Function, that generates the following further leads, such as

- cytokine activity
- growth factor activity
- interleukin-6 receptor binding

2- Biological process search will yield the processes where IL-6 mediates are enumerated as follows:

- acute-phase response
- cellular protein metabolic process
- cellular response to hydrogen peroxide
- cellular response to lipopolysaccharide
- cytokine-mediated signalling pathway
- endocrine pancreas development
- glucagon secretion
- hepatic immune response
- humoral immune response
- inflammatory response
- interleukin-6-mediated signalling pathway
- maintenance of permeability of blood-brain barrier
- monocyte chemotaxis
- negative regulation of apoptotic process
- negative regulation of bone resorption
- negative regulation of cell population proliferation
- negative regulation of chemokine biosynthetic process
- negative regulation of collagen biosynthetic process
- negative regulation of fat cell differentiation
- negative regulation of interleukin-1-mediated signalling pathway
- negative regulation of lipid storage
- neuron cellular homeostasis
- neuron projection development
- neutrophil apoptotic process
- neutrophil mediated immunity
- platelet activation
- positive regulation of acute inflammatory response
- positive regulation of apoptotic DNA fragmentation
- positive regulation of apoptotic process
- positive regulation of B cell activation
- positive regulation of cell population proliferation
- positive regulation of chemokine production
- positive regulation of DNA-binding transcription factor activity

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- positive regulation of epithelial to mesenchymal transition
- positive regulation of extracellular matrix disassembly
- positive regulation of gene expression
- positive regulation of glial cell proliferation
- positive regulation of immunoglobulin secretion
- positive regulation of interleukin-17 biosynthetic process
- positive regulation of interleukin-6 production
- positive regulation of leukocyte chemotaxis
- positive regulation of MAPK cascade
- positive regulation of neuroinflammatory response
- positive regulation of osteoblast differentiation
- positive regulation of peptidyl-serine phosphorylation
- positive regulation of smooth muscle cell proliferation
- positive regulation of T cell proliferation
- positive regulation of T-helper 2 cell cytokine production
- positive regulation of transcription, DNA-templated
- positive regulation of transcription by RNA polymerase II
- positive regulation of translation
- positive regulation of type B pancreatic cell apoptotic process
- positive regulation of vascular endothelial growth factor production
- post-translational protein modification
- regulation of angiogenesis
- regulation of astrocyte activation
- regulation of microglial cell activation
- regulation of neuroinflammatory response
- regulation of vascular endothelial growth factor production
- response to glucocorticoid
- T-helper 17 cell lineage commitment

A linear computer search yields random non-serialized progression of data as listed above. Each of the above will generate one or more leads that get integrated into numerous metabolic processes. The process is tedious, time consuming and will need integration with in-depth understanding of the process. In contrast, bioinformatics with its unique, refined software tools will process all of the above to give a result in the form of processes in progress chart. This chart will indicate the genes responsible for protein production such as STAT3 and will also include the proteins that constitute a receptor binding site such as EBS. Thus bioinformatics generates composite information concerning this scientific knowledge based on technology of gene expression of DNA, proteomics [7].

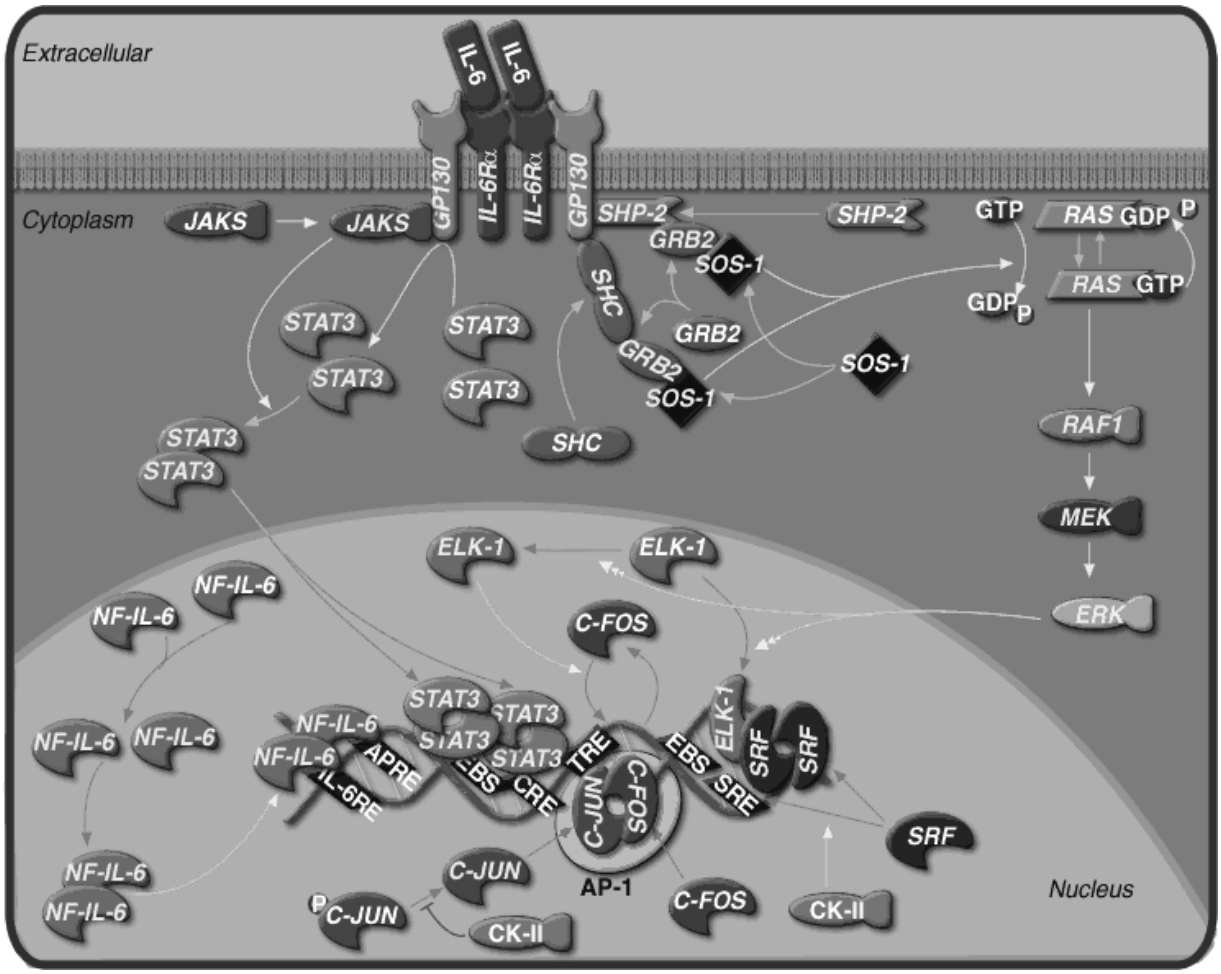

Fig. 1: https://data.broadinstitute.org/gsea-msigdb/msigdb/biocarta/human/h_il6Pathway.gif[6]

Melanin synthesis involves approx. 1500 proteins. Melanogenesis, in turn is influenced by several intrinsic factors such as molecules secreted by surrounding keratinocytes, fibroblasts, neural or endocrine cells. [8]

Focalization was arrived by consideration of the following factors:

1. Hair is ectodermal tissue.
2. Melanin is secreted by melanocytes that are regulated by melanocyte-stimulating hormones secreted by the skin, pituitary gland and hypothalamus. Endogenous secretions originate from endodermal tissue.
3. Mesenchymal Stem Cells are derived from the mesenchymal tissue.

We further focalize on IL-6 as one of the prime cytokines secreted by MSCs. It was selected for following reasons:

1. Endocrine pancreas development
2. Glucagon secretion
3. Interleukin-6-mediated signalling pathway
4. Negative regulation of bone resorption
5. Neuron cellular homeostasis
6. Positive regulation of epithelial to mesenchymal transition
7. Positive regulation of osteoblast differentiation
8. High expression of CD44 marker[9]

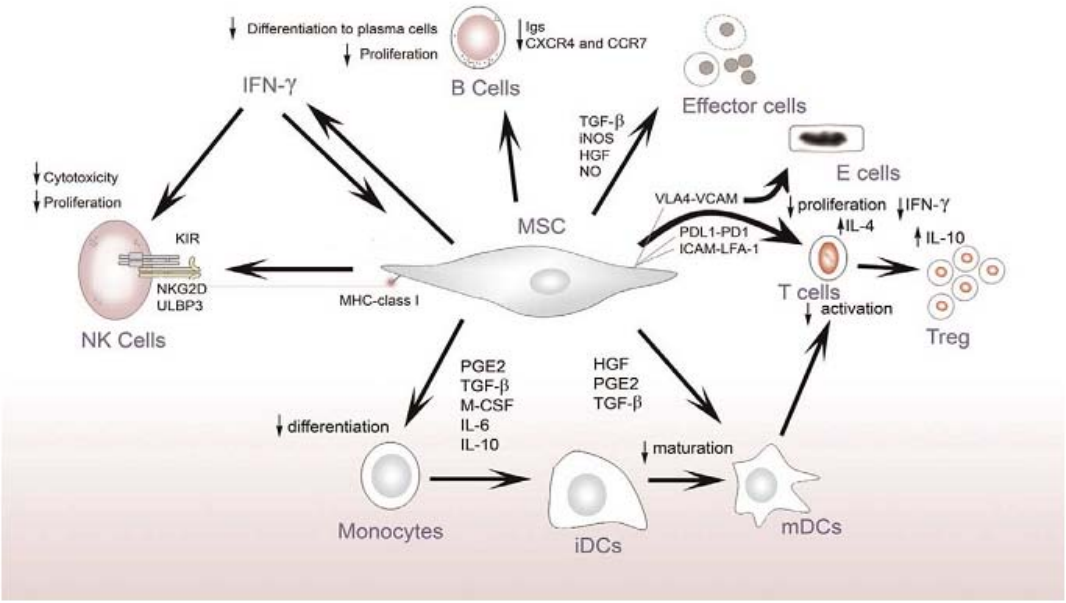

Fig. 2: Bioinformatics of mesenchymal stem cells

Legend:
NK Cells – Natural Killer Cells
KIR - Killer cell immunoglobulin-like receptors
ULBP3 - UL16-binding protein 3
IFNγ - Interferon gamma
MHC - major histocompatibility complex
PGE2 - Prostaglandin E2
TGF-β - Transforming growth factor beta
M-CSF – Macrophage Colony stimulating factor
IL – Interleukin
Igs – immunoglobulin
CXCR-4 - C-X-C chemokine receptor type 4
CCR-7 - C-C chemokine receptor type 7
iNOS – Nitric Oxide Synthase
HGF – Hepatocyte Growth Factor
PDL 1 - Programmed death-ligand 1
PD1 - Programmed cell death protein 1
ICAM - Intercellular Adhesion Molecule

Simplified bioinformatics chart (Fig. 2) arrived at the following properties as derived from various molecules as expressed by MSCs:

1) Multilineage translation
2) Facility to migrate to affected tissue and translate to it
3) Anti inflammatory property by virtue of paracrine secretions
4) Regenerative capability
5) They are HLA-DR negative, which makes them immunonaive.

Indian Council of Medical Research and Drug Controller General of India informed.

III. Results

Spindle shaped cells with a large molecule suggested a phenotype of BM-MSCs. This was verified with positive CD44 marker at National Centre for Cell Biology, Pune.

ADMSCs were verified with 4 positive markers, CD 44, CD 105, CD29 and CD 90 [Fig.3]

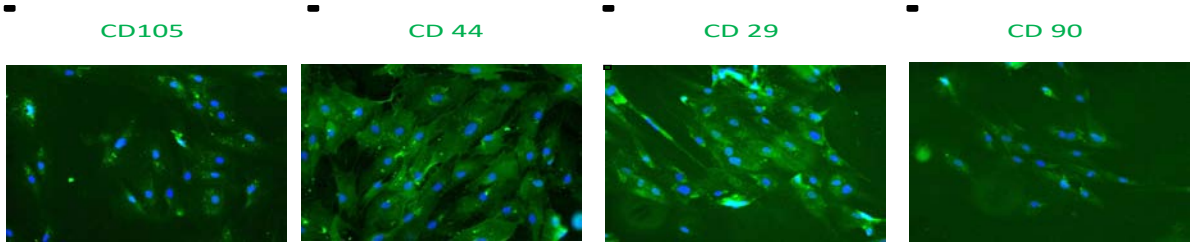

Fig. 3: CD positive markers CD105, CD44, CD29 and CD90.

ADMSCs were translated to a neuronal cell [Fig.4], Insulin secreting cell [Fig.5] and chondrocytes [Fig.6].

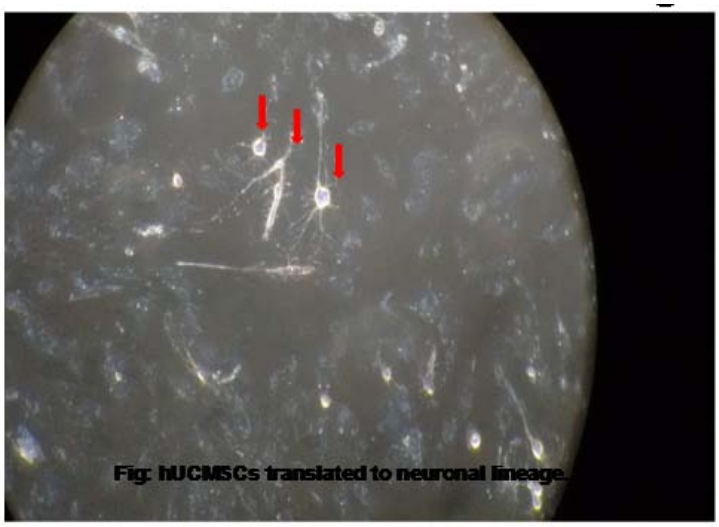

Fig. 4: Translation to neuronal cell

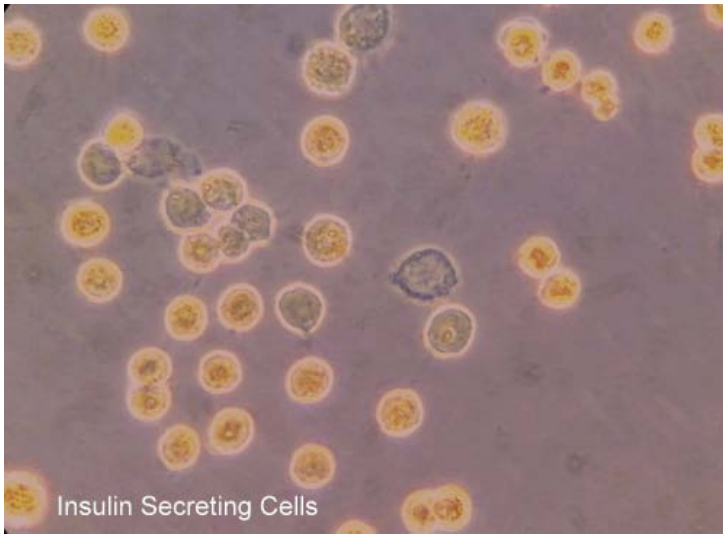

Fig. 5: Translation to Insulin secreting cell

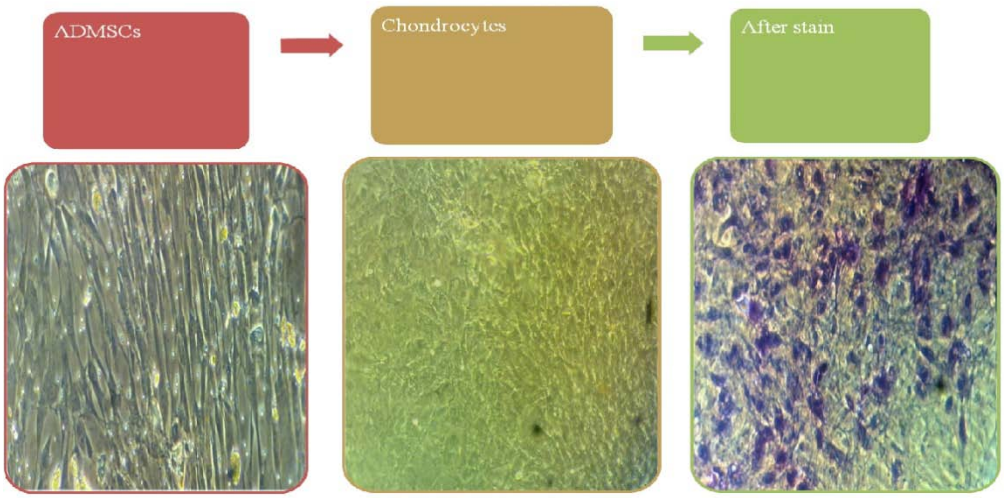

Fig. 6: Translation to chondrocytes

This yielded a proof of concept for preliminary clinical trial for application to degenerative neuronal conditions, diabetes mellitus: Type 1, Type 2, Maturity Onset Diabetes of Young Adults [4] and Osteoarthritis [3].

ICMR and DCGI notify that Stromal Vascular Fraction and MSCs are drugs that need to be investigated further.

IV. Discussion

While researching in a preliminary clinical mode, application of MSCs to diverse degenerative neurological conditions, an accidental finding of grey hair turning to black was observed. This paper highlights that howsoever ambiguous a finding in research, it should not be given a pass. Nature may appear to be playing dice but it does not.

Had Alexander Fleming given a pass to a chance non-occurrence of microbial growth in a particular Petri dish, penicillin may not have been discovered. Therefore, every occurrence, howsoever trivial, must be explained. Researchers usually publish positive results. We should derive inference as to how 10 of the 14 patients did not show the positive signs.

This accidental finding has charted a pathway to possible new drug discoveries. The process will take long to go through various stages of clinical trials. Yet, it is established, with additional evidence as presented in this research that it is plausible that ADMSCs may be a futuristic drug.

The paper also highlights how bioinformatics shortens the processes that would have taken a long time to establish in a wet lab.

V. Conclusion

The paper highlights that accidental findings do have a process that would have generated the occurrence. The process in melanogenesis involves all 3 germinal layers. That paved the way to a plausible clinical application of ADMSCs to apparently diverse appearing clinical conditions.

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