Evenimente biologice ale melanocitului normal tranformat neoplazic in melanom - puncte nodale în medicina personalizată

Events in the journey of a normal melanocyte transformed into a skin melanoma – key points in personalized medicine

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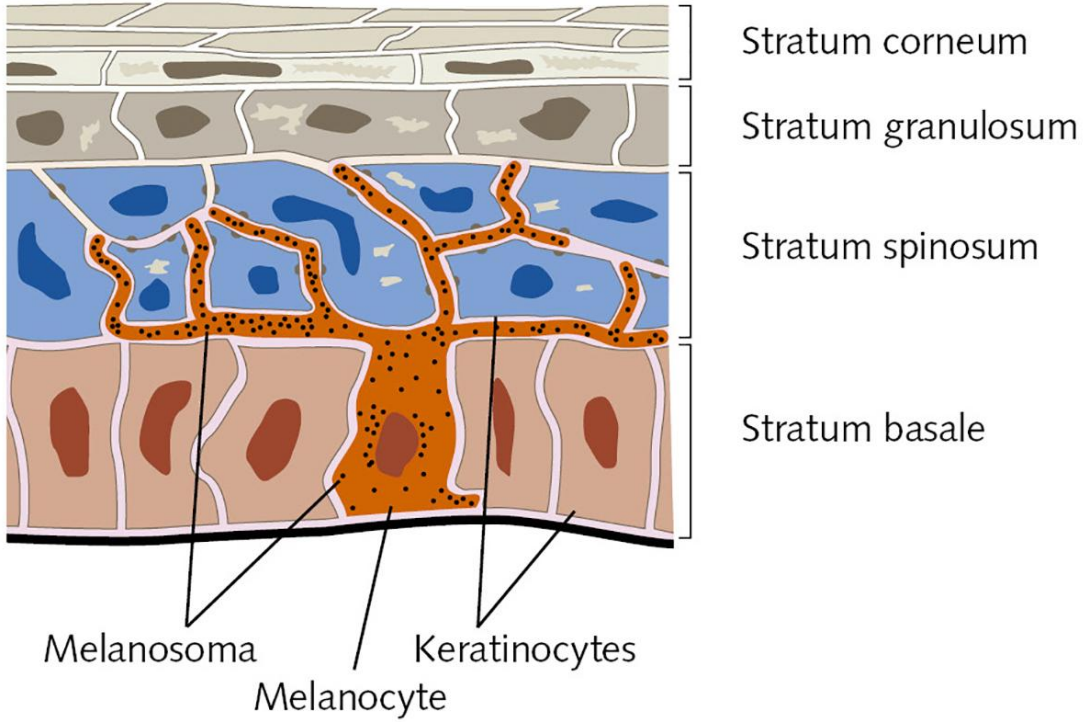
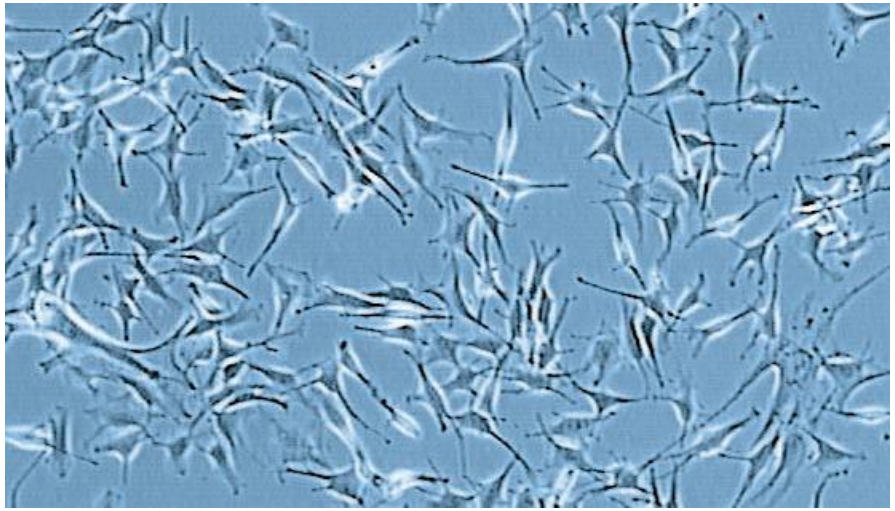
Cellular identity of a normal melanocyte





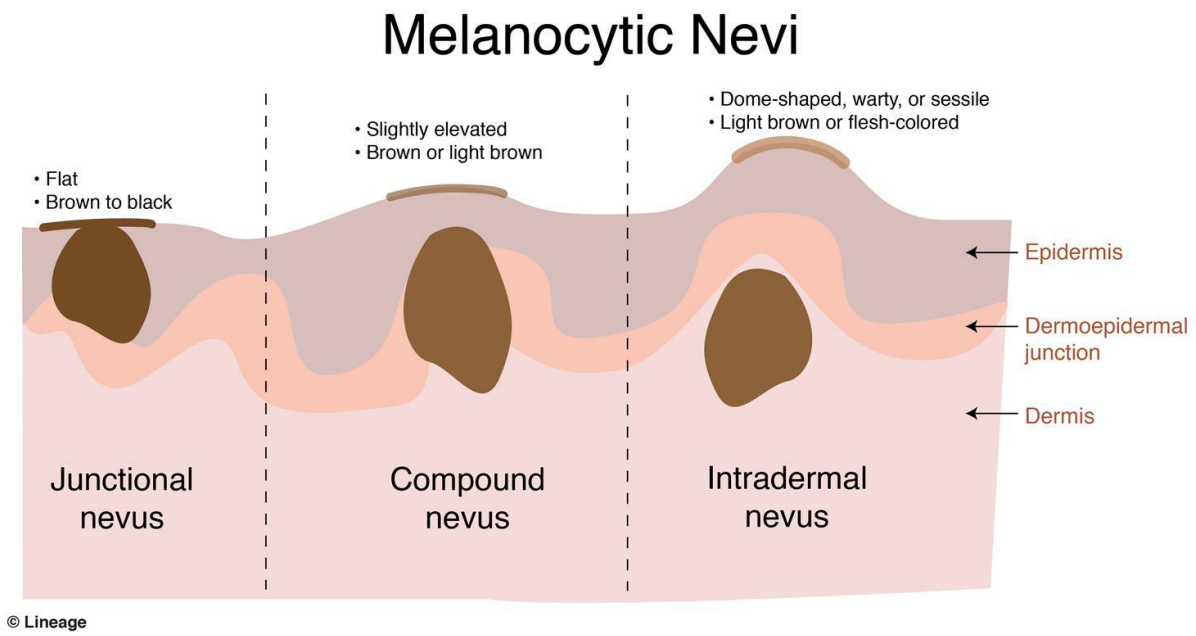
NHEM2 cells

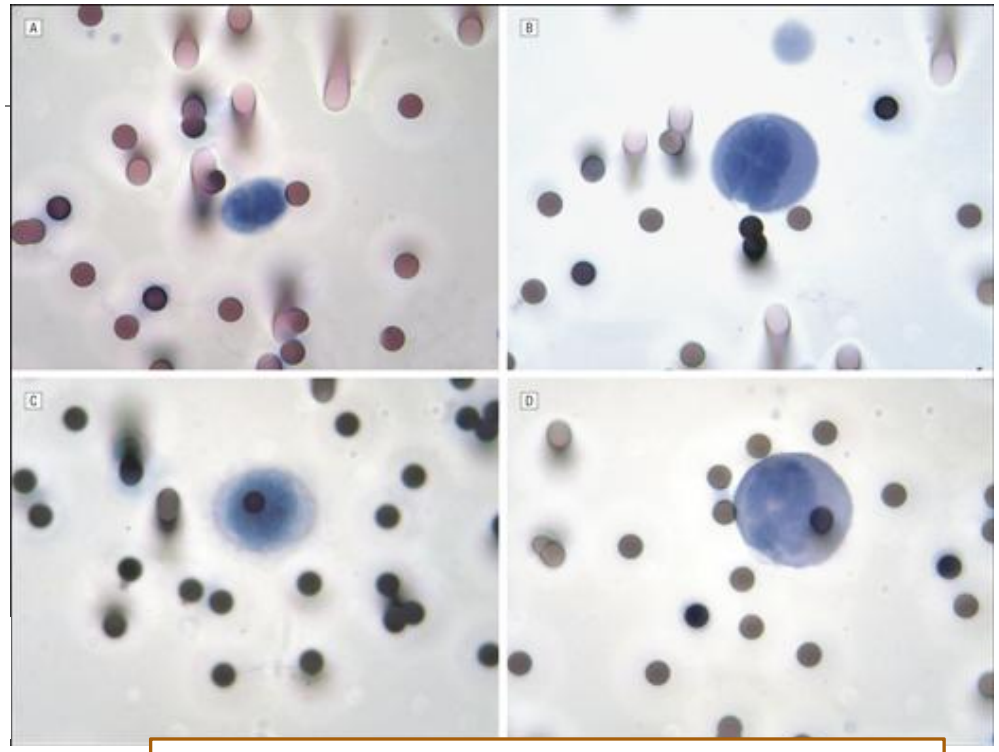
Cellular identity of a normal melanocyte

- Normal melanocytes – expression of Pax3, Sox10, endothelin3 (ED-3), specific receptor (Endrb), c-Kit and Mitf ;
- p53 activation in keratinocytes upon UVR induces proopiomelanocortin (POMC) transcription, precursor for α MSH and ACTH, hormones that have pro-pigmenting properties (Cuit et al., 2007).
- α MSH activates MC1R that increase MITF - key proteomic marker for melanocytes, linked to pigment production and melanin synthesis. MITF regulates genes that induce melanosome biogenesis (Hoek et al., 2008), melanin synthesis and melanosome trafficking (Chiaverini et al., 2008), sustaining the photoprotection of the skin (Walker et al., 2009).
- Keratinocyte release α MSH, endothelin, GM-CSF, leukemia inhibitory factor - LIF, basic fibroblast growth factor - bFGF, hepatocyte growth factor - HGF that induce melanocyte proliferation (Hirobe, 2005).
- Normal melanocytes have anti-apoptotic mechanisms resisting to the UV-induced DNA damage. Upon UV, MITF expression is increased and several anti-apoptotic genes expression are involved, such as BCL2, BCL2A1, ML-IAP along with the up-regulation of genes involved in DNA repair (Haqa et al., 2013, Strub et al., 2011).

Monica Neagu**,** Carolina Constantin, Basak Engin, Iulia Popescu, Snapshot – changing melanocyte identity in melanoma developing route, *Journal of Cell Identity*, vol. 1, p. 0033-0047, October, 20, 2020

Melanocytes comprised in benign nevi





Circulating benign melanocytes

Melanocytes comprised in benign nevi

- Melanocytes within melanocytic nevi have proteomic and genomic particularities.

- The majority of human, congenital melanocytic nevi have NRASQ61K/R mutations and the majority of acquired nevi have BRAFV600E mutation. In all the tested nevi we found various BRAF mutations and in some of them NRAS

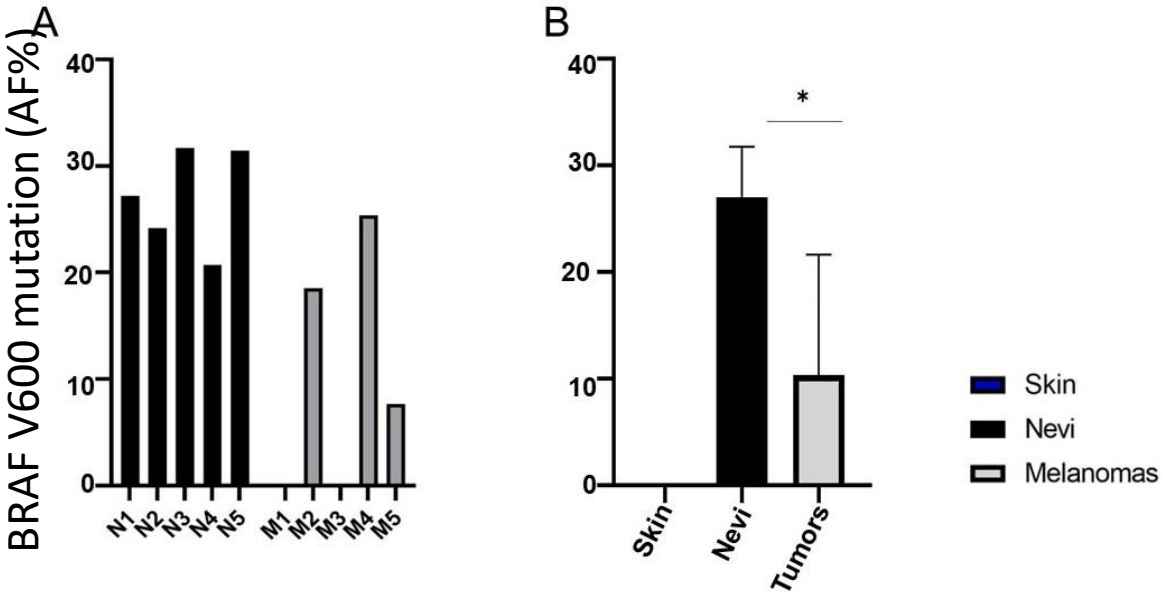
- When oncogenic NRAS or BRAF are induced to be over-expressed in normal melanocytes a senescence phenotype is triggered - melanocytes within the nevi can have the cellular growth arrested for tens of years (Ruiz-Vega 2020). We have shown also that nevi do not express proteins appended to cell cycle (e.g.cyclins).

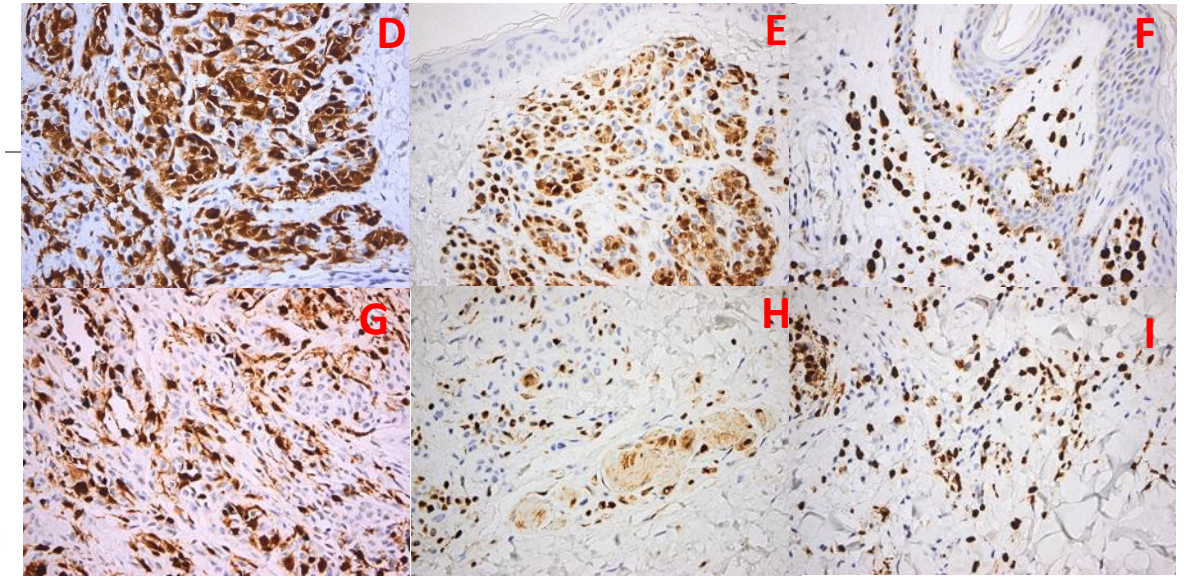
- Benign melanocytes with NRASQ61K or BRAFV600E mutations rarely progress to melanoma.

- But if several regulatory proteins are missing (lacking of p16INK4a, Pten or β -catenin) melanomagenesis will be accelerated.

- Various genetic/epigenetic modifications along with various extrinsic stimuli would drive melanoma development (Damsky et al., 2015).

BRAF V600 mutation allele frequency (AF%) in nevi vs melanoma



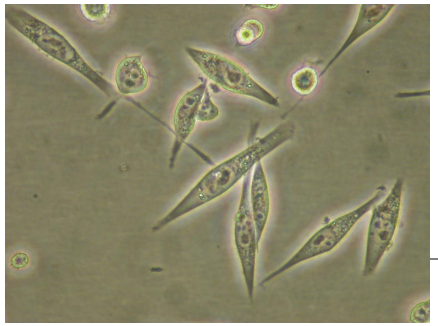


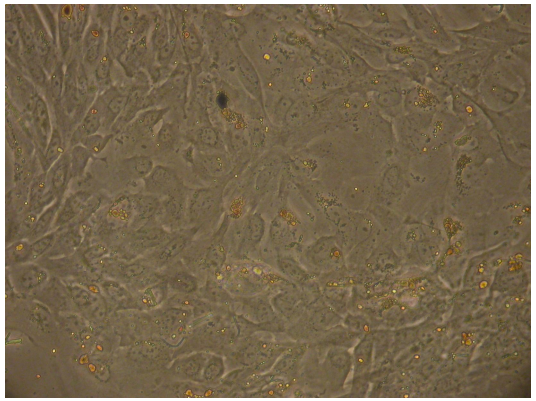
p16 expression in Papillomatous intradermal nevocellular nevus; D-F. 16 positivity of the tumor cells in the upper dermis: numerous cells with strong cytoplasmic and nuclear positivity. P16 x 400. G-I. Less numerous tumor cells positive for p16 in the deep dermis than in the superficial areas; preservation of both cytoplasmic and nuclear expression. P16x400

Elena-Georgiana Dobre, Carolina Constantin, Monica Neagu, Skin Cancer Research Goes Digital: Looking for Biomarkers within the Droplets, *J. Pers. Med*. 2022, 12(7), 1136; https://doi.org/10.3390/jpm12071136.

Georgiana-Elena Dobre, Luciana Nichita, Cristiana Popp, Sabina Zurac, Monica Neagu, Assessment of the pro-inflammatory EGFR-RAS-RAF pathway mutation status in healthy skin, benign nevi, and cutaneous melanomas: pilot study, *Journal of Inflammation Research* 2023 (*in press*)

Melanomagenesis

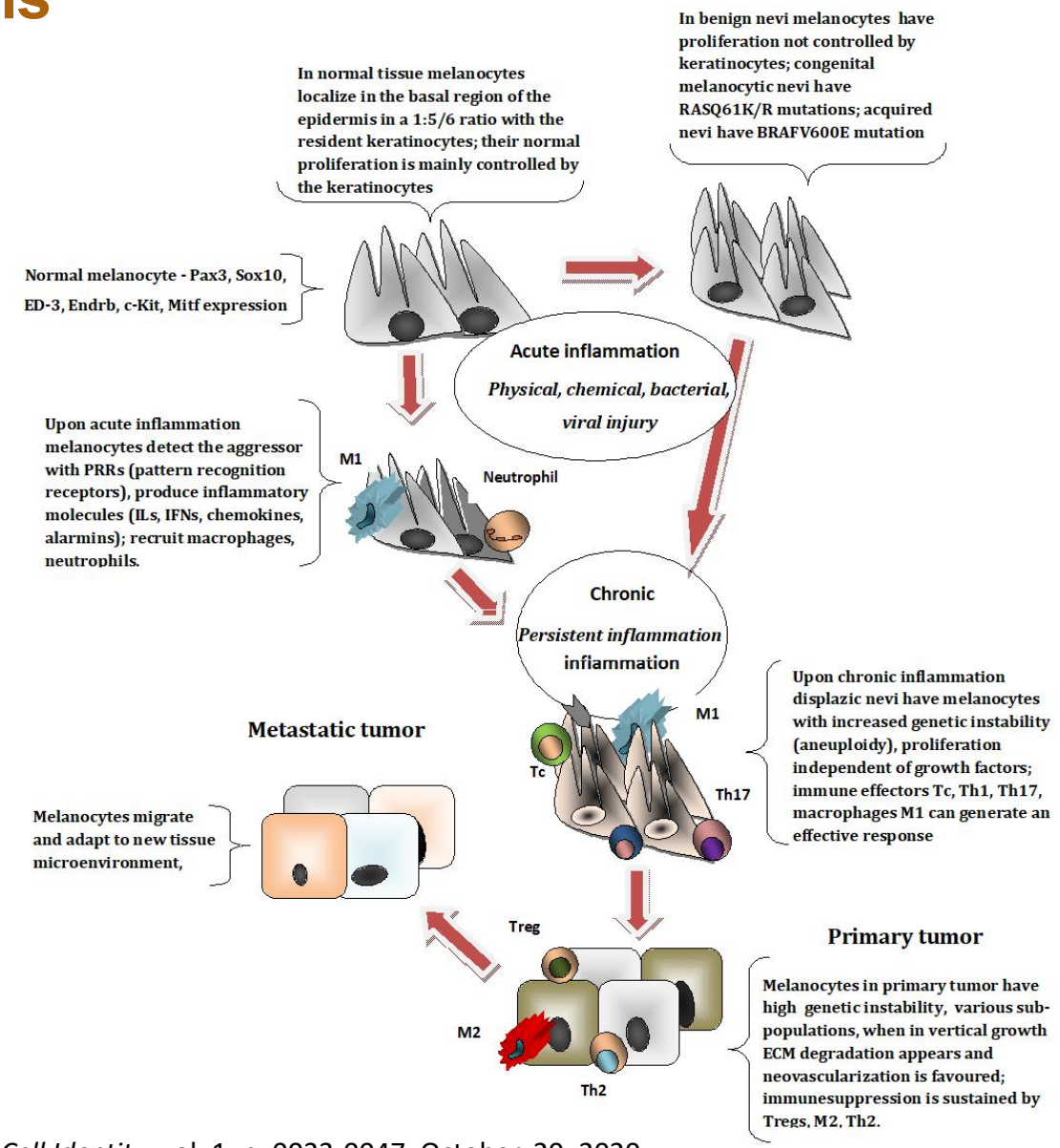




Inflammation Environment

Metabolism

Neuroendocrine factors



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Monica Neagu et al, Langerhans Cells-Revising Their Role in Skin Pathologies, *J Pers Medicine*, 12(12), 2072, 2022, doi:10.3390/jpm12122072

Melanomagenesis

Inflammation Environment

- Immune cells proportion - inflammatory pattern of the tumor and characterizes the balance between an efficient local anti-tumor response and a pro- tumor millieu (Zurac et al., 2013; Neagu et al., 2019);
- The newly created TME contributes to establishing an immunosuppressive network (Neagu et al, 2015). In this network, stromal cells interrelate with inflammatory immune cells and vascular system cells. The molecular pattern of TME abounds in molecules like cytokines, chemokines and growth factors that sustain the tumor immune escape;
- Two distinct mechanisms of resistance: existence of immune-suppressive cells and the lack of active immune cells. When tumors have a high infiltration of Treg, B cells and MQ an immune-suppressive cellular milieu is developed (Neagu et al., 2019); specific NK cells that infiltrate melanoma can induce in the TME an EMT processes inducing thus a more aggressive tumor cell phenotype (Izvoranu et al, 2021, Neagu et al., 2019);
- A chronic inflammation, long-term production and accumulation of inflammatory factors (e.g. cytokines/chemokines) can induce locally/systemically immunosuppression milieu associated with cancer progression (Neagu et al., 2013, Neagu et al., 2015).
- The circulatory levels of IL-6, IL-8 can pinpoint the overall inflammatory status of a developing melanoma. In animal models (Surcel et al., 2017) and in patients (Ene et al., 2015) IL-6, IL-8 is significantly increased and correlated to the clinical evolution of the disease.

Melanomagenesis

Metabolic traits of melanomagenesis

- Metabolic deregulations gain increased significance.

- A normal and a tumor cell have divergent metabolic status. The tumor cell has an altered metabolism and thus various different metabolic markers; the metabolism of a tumor cell has to be more dynamic, needs an increased metabolic flux and more nutritional factors. This metabolism is required to support an accelerated cell proliferation, to sustain migration, to survive in hypoxia conditions and to adapt to different tissue environments when engaged in metastasis (Neagu, 2020).

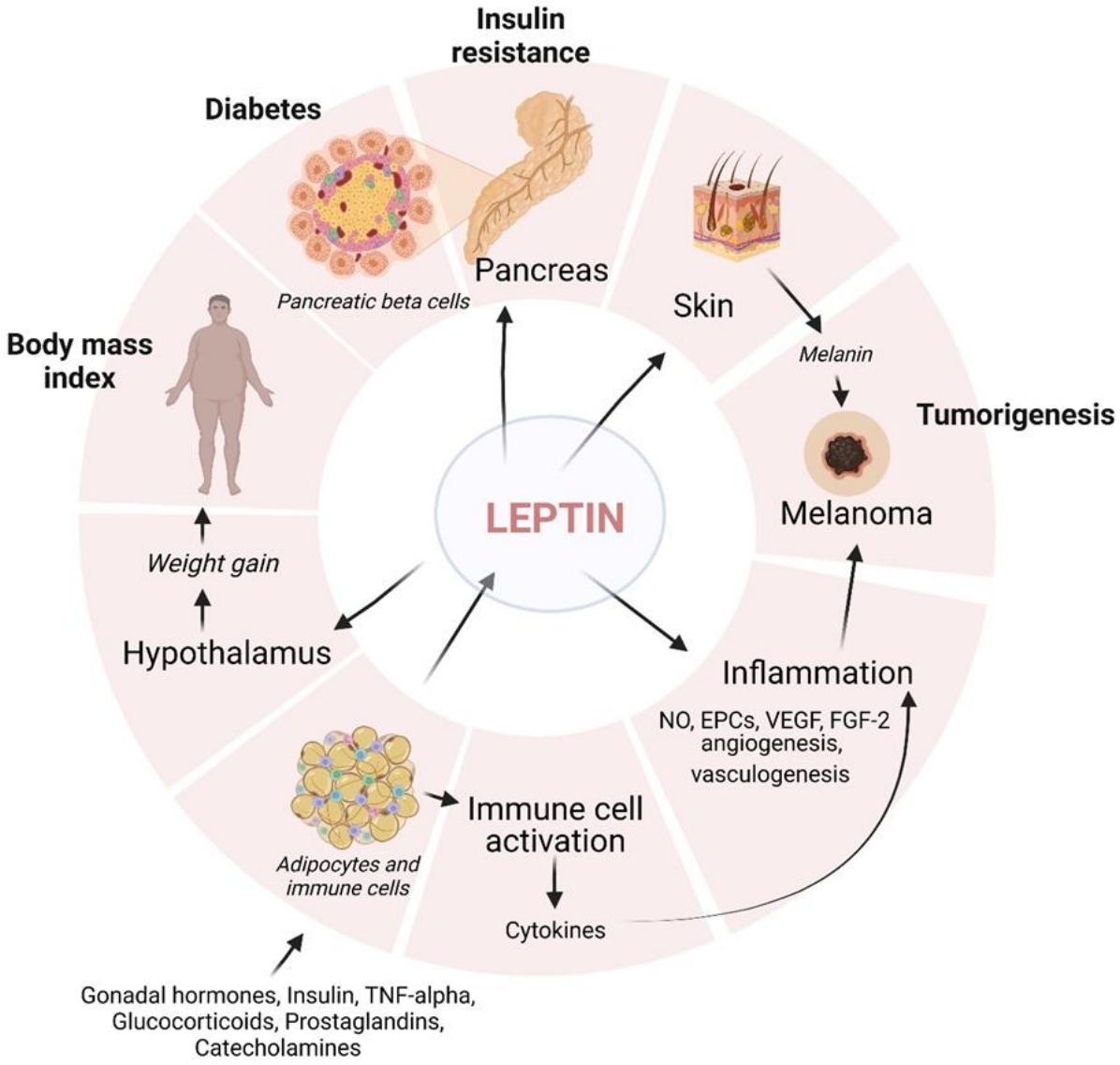
- Tumor cell metabolism would generate increased lactate production, NO, ROS and arachidonic acid by-products (prostaglandins) - inflammatory milieu and a tumor-permissive environment (Netea-Maier et al., 2018). The abnormal metabolism induces the expression of various dysfunctional proteins enhancing the pro-tumorigenic mechanisms. Therefore, tumor cell metabolism will lead to a deregulated cell cycle, enhanced anti-apoptotic cellular patterns, decreased cell death, increased migratory capacity and high adaptability to various non-related tissue microenvironment (Wang et al., 2018).

- In melanoma, glucose metabolism is the main deregulated metabolic cycle, leading to protein and gene deregulations (Gentric et al., 2017). As the main fuel controlling organelle, mitochondria, is highly involved in tumorigenesis through various pathways and metabolic alterations as decreased oxidative phosphorylation (OXPHOS) and anabolic pathways induction. Mitochondria controls ROS levels, DNA mutations, namely genomic instability, it controls autophagy and resistance to cell death stimuli (Masgras et al., 2017; Neagu et al., 2019, Berdiaki et al, 2023).

Melanomagenesis

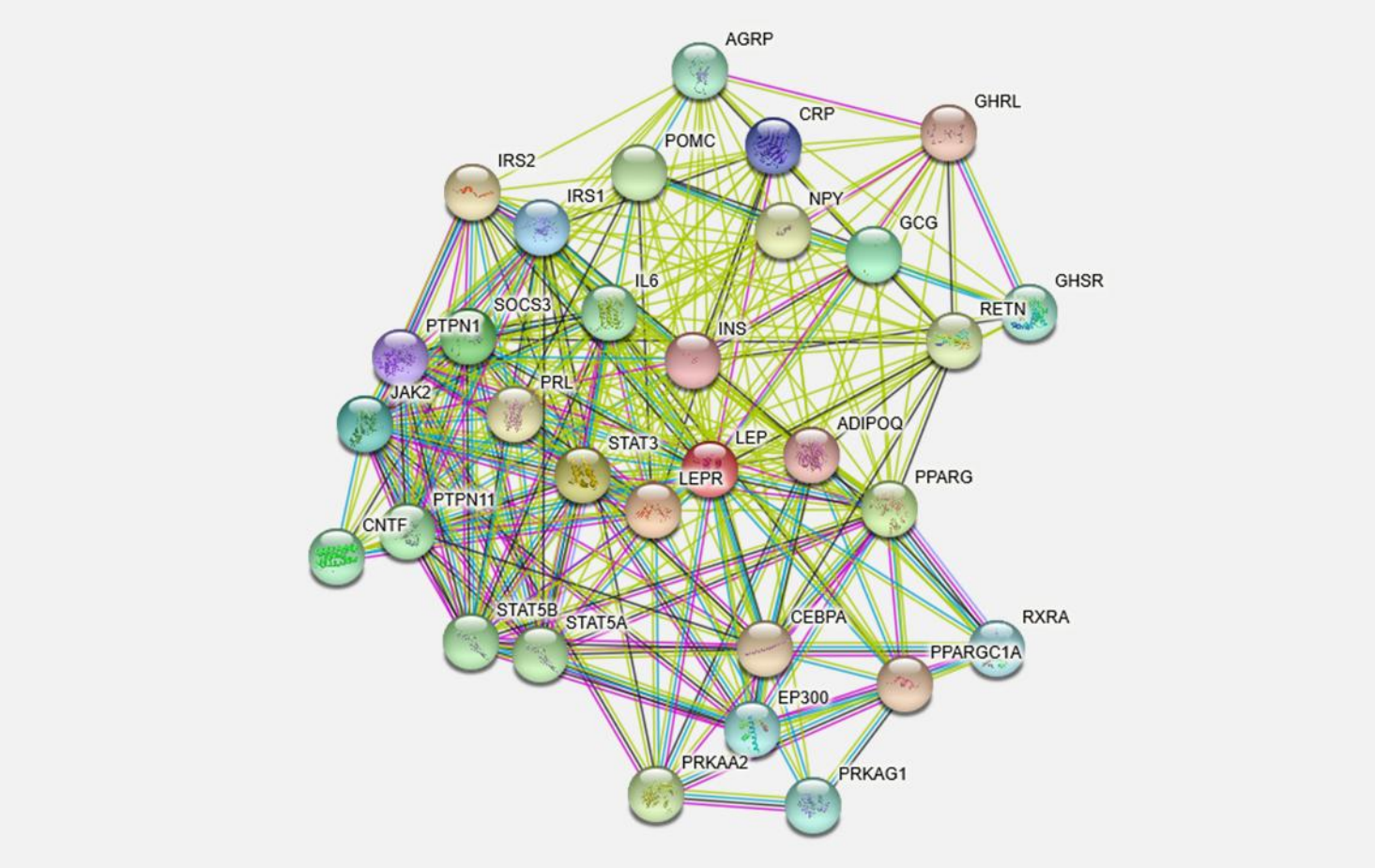
Neuroendocrine "influencers" of melanomagenesis

- In the skin there is an array of neuroendocrine factors that are involved in various physiological and pathophysiological processes (Caruntu et al., 2014).
- Cathecolamines can induce melanoma progression and can stimulate melanoma cell proliferation through beta-adrenergic receptors activation (Janik et al., 2017, Caruntu et al., 2014).
- It seems that melanoma cell have different receptors expression and hence susceptibility to respond to adrenaline. Thus, depending on the origin and progression stage, metastatic skin melanoma cells are less responsive to adrenaline, while primary skin and uveal melanoma cells are more sensitive (Janik et al, 2017).
- We have shown on murine melanoma cell lines that exposure to high concentrations of epinephrine and norepinephrine induces a significant increase in cell proliferation (Caruntu et al, 2014). There are different expression of specific receptors depending on the melanoma origin, thus in human melanoma cell lines we have shown that the proliferative action triggered by epinephrine and nor-epinephrine can be overridden by some of specific inhibitors (Surcel et al., 2018).
- Leptine, a hormone involved in lipid metabolism can trigger inflammation and have pro-tumoral activity in melanoma (Neagu, 2020, Constantin, 2022).



Monica Neagu , Georgiana Dobre, New insights in the link between melanoma and obesity, *Adv Exp Med and Biol*, in Springer Series Obesity, 2023 (in press)

Circulating leptin in melanoma patients



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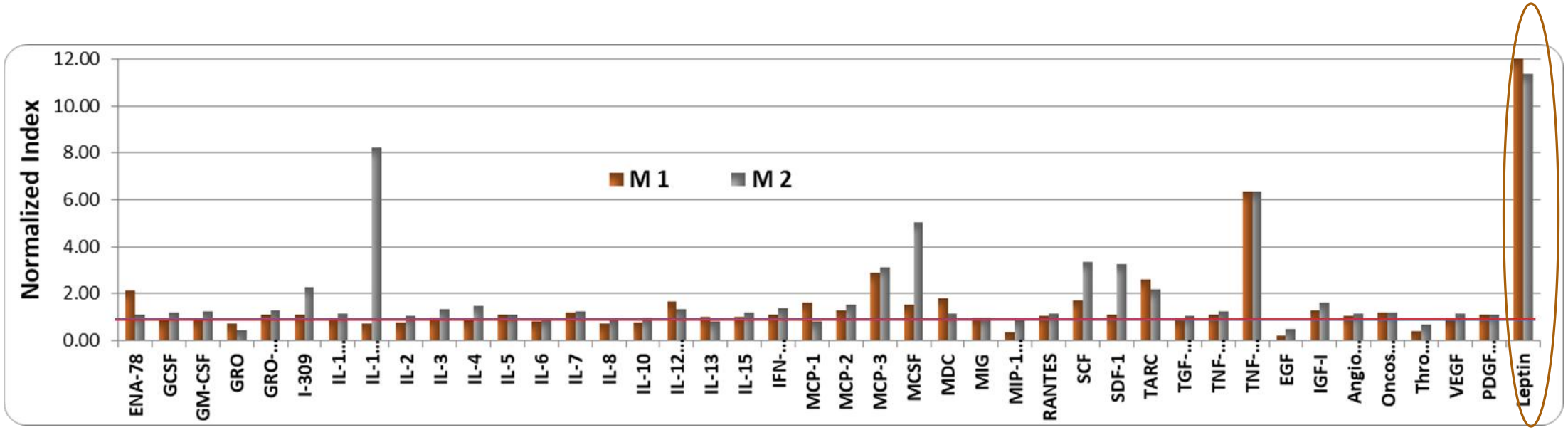

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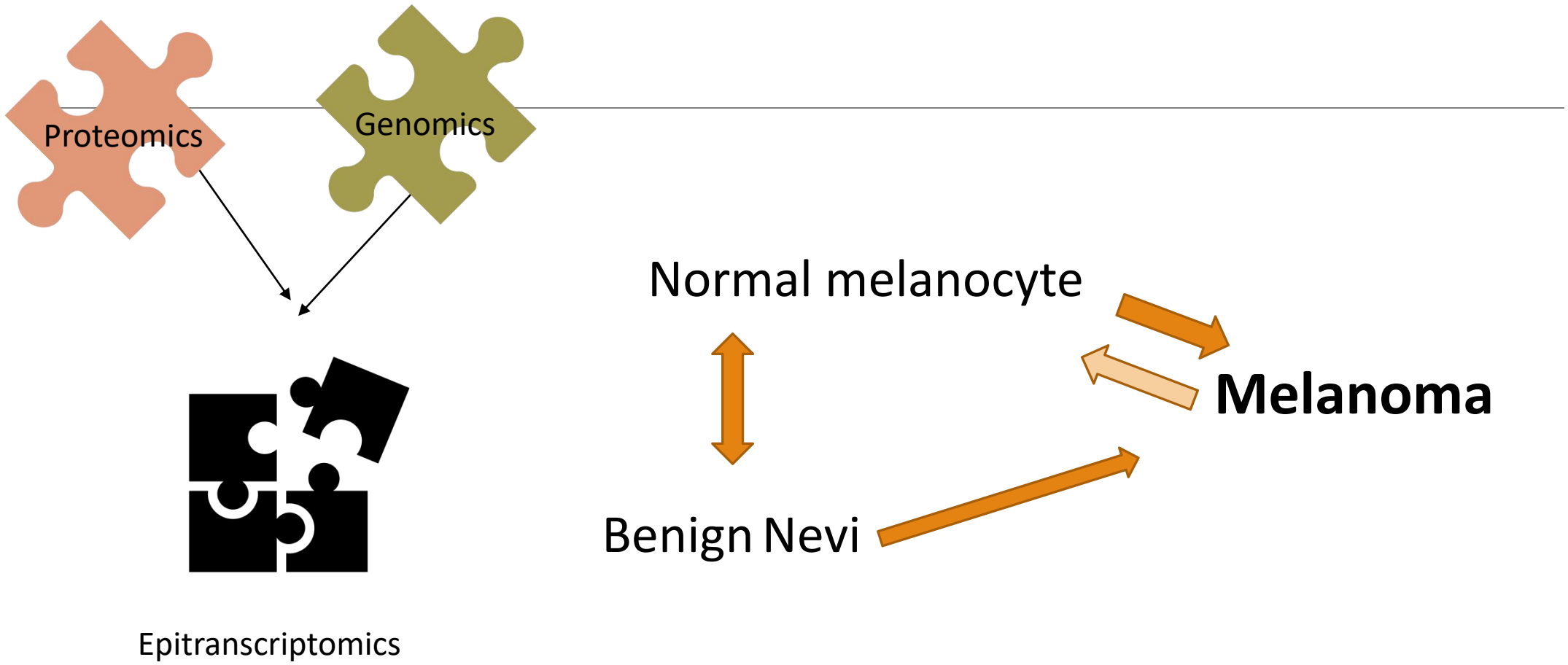
Take home notes



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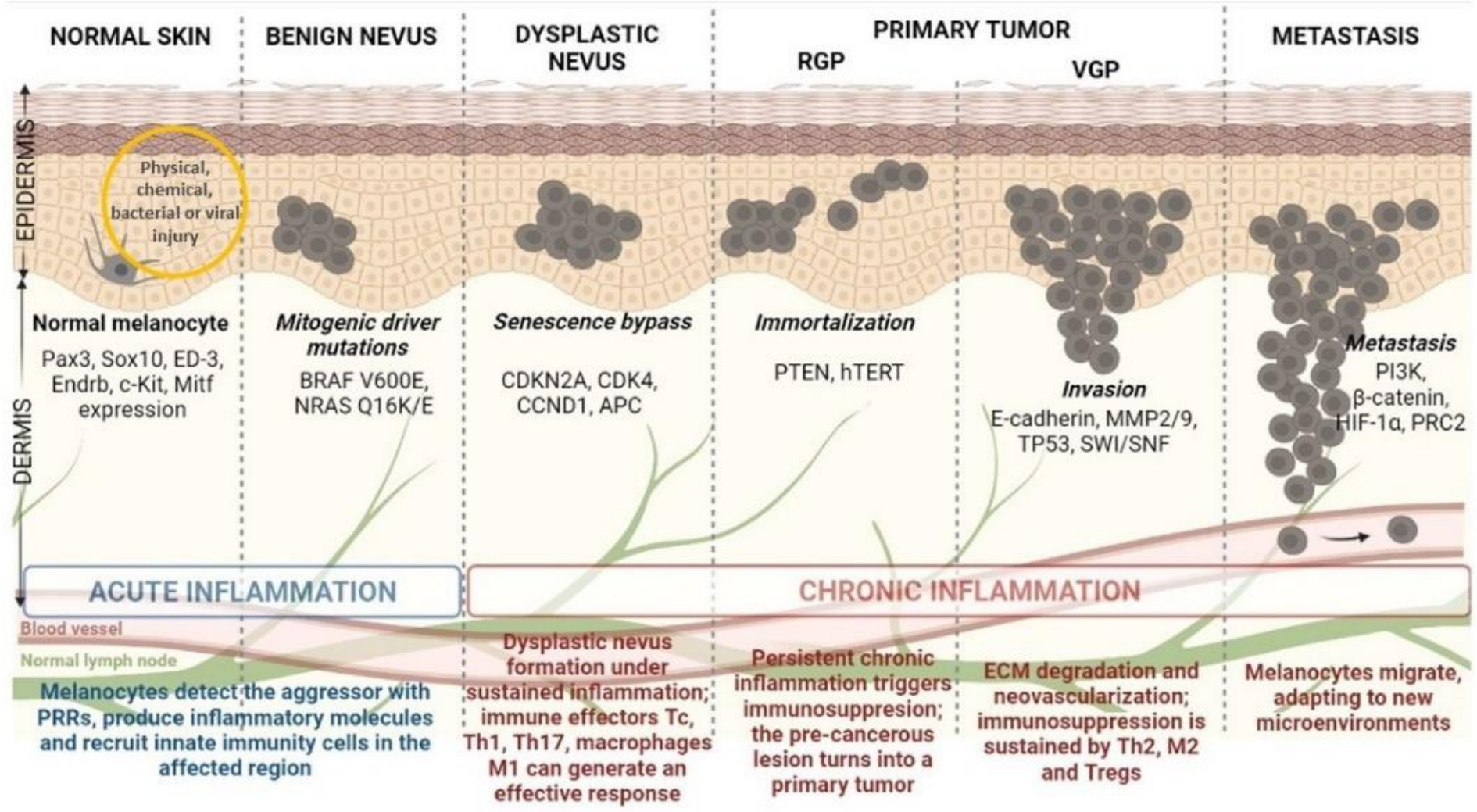
Take home notes



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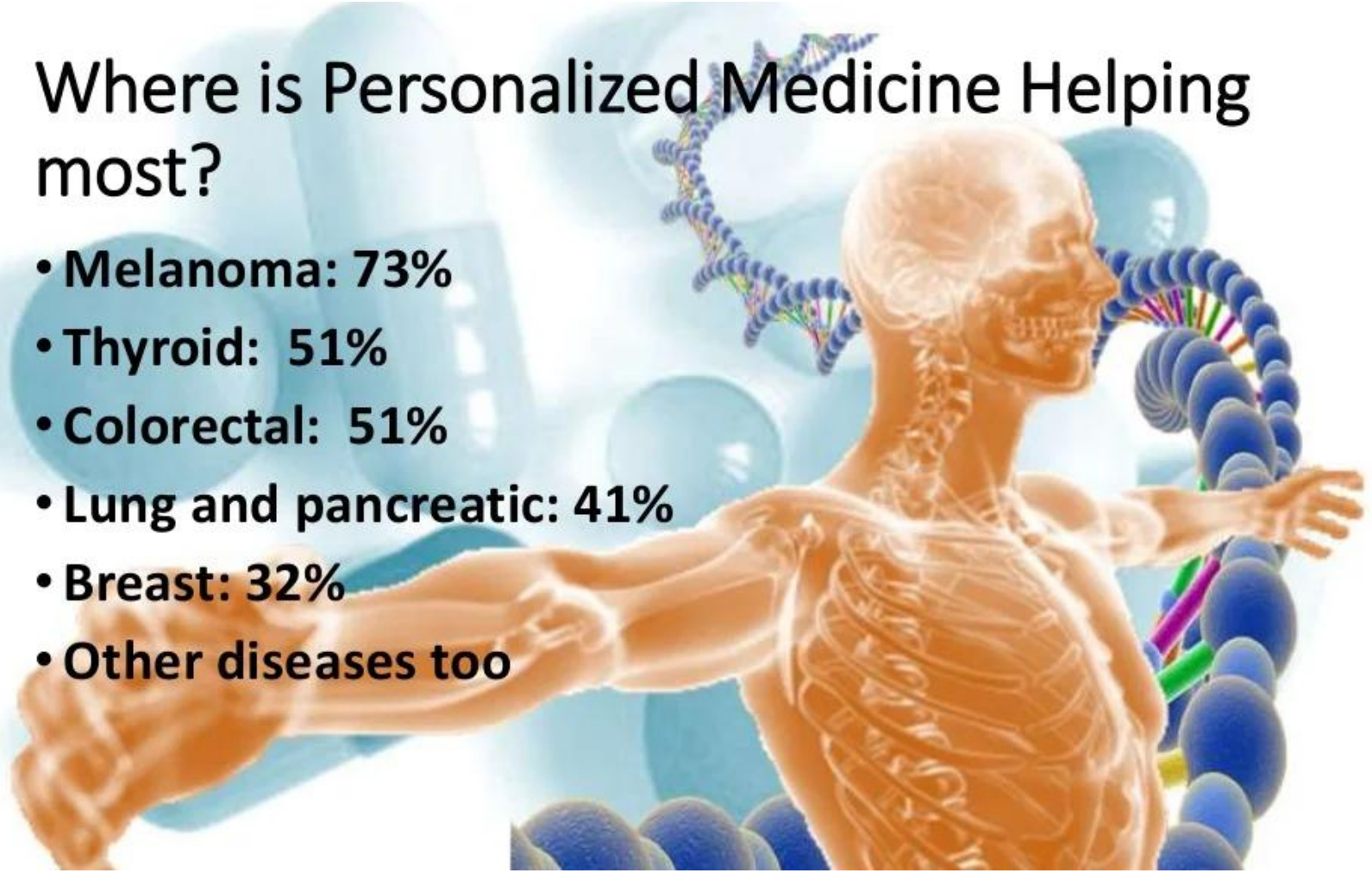
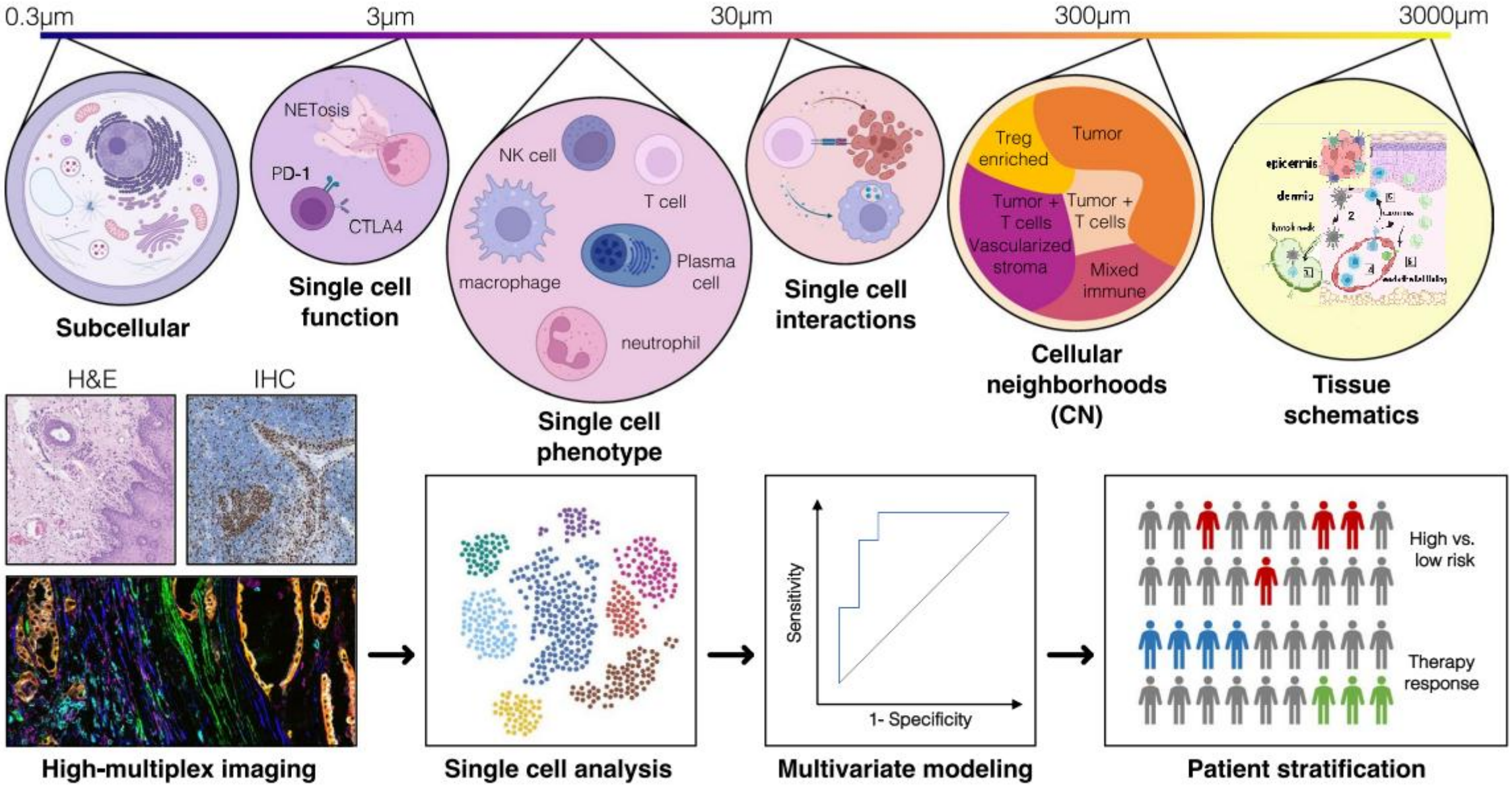
Where is Personalized Medicine Helping most?

- Melanoma: 73%
- Thyroid: 51%
- Colorectal: 51%
- Lung and pancreatic: 41%
- Breast: 32%
- Other diseases too



Jakob Einhaus et al, High- multiplex tissue imaging in routine pathology—are we there yet? *Virchows Archiv*, 2023



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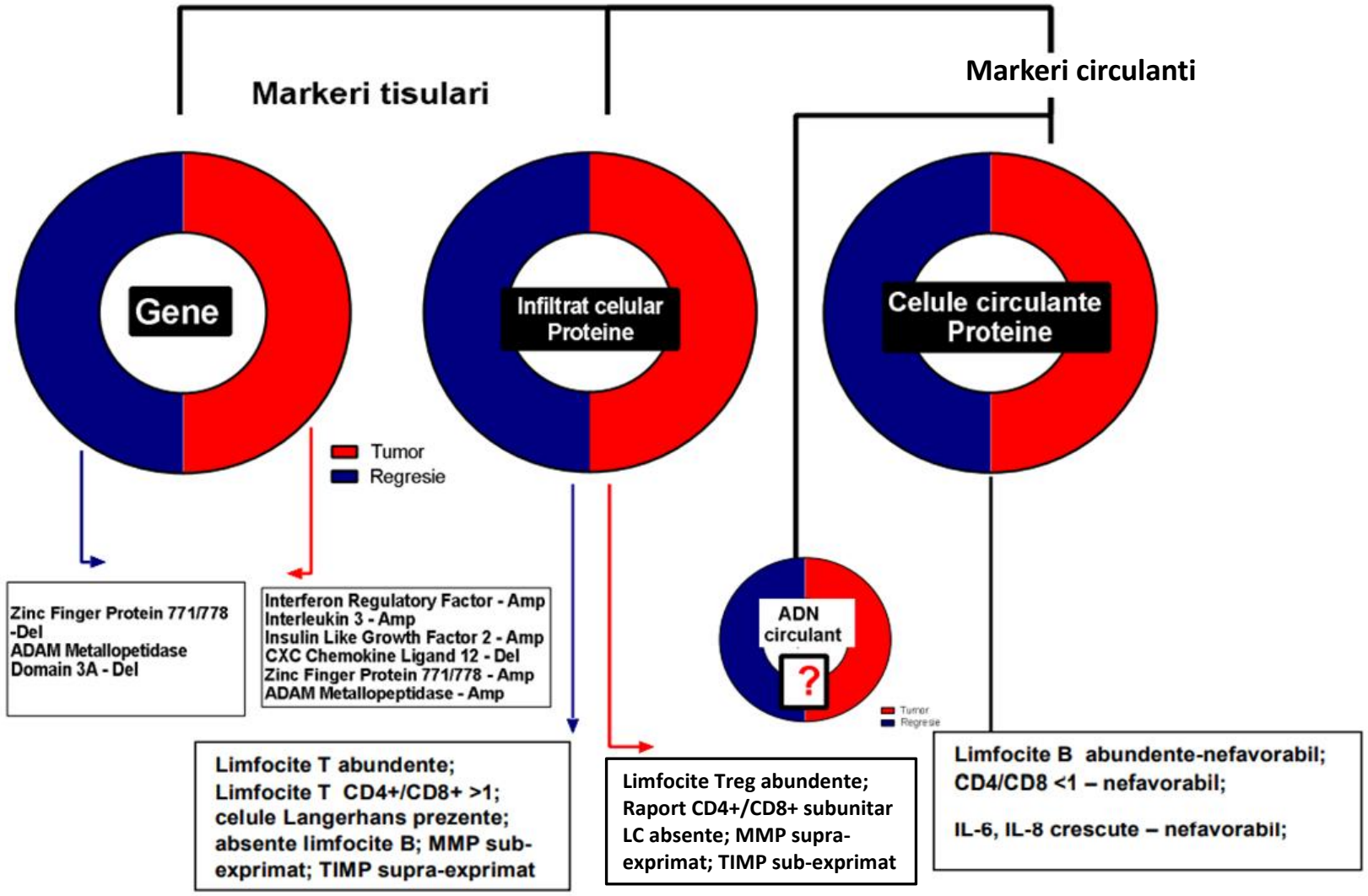
Propunere de clasificator teranostic polifactorial



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COST Action CA21108 - European Network for Skin Engineering and Modeling (NetSkinModels) (2023-2026)

Thank you!
Multumesc!

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