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Malignant Melanoma: Autoimmunity and Supracellular Messaging as New Therapeutic Approaches

Ion G. Motofei, MD, PhD

Address
Department of Surgery/Oncology, St. Pantelimon Hospital, Carol Davila University, Dionisie Lupu Street, no. 37, 020022, Bucharest, Romania
Email: igmotofei@scholar.ro

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Opinion statement

Melanoma is one of the most aggressive forms of cancer, with a high mortality rate in the absence of a safe and curable therapy. As a consequence, several procedures have been tested over time, with the most recent (immunological and targeted) therapies proving to be effective in some patients. Unfortunately, these new treatment options continue to generate debate related to the therapeutic strategy (intended to maximize the long-term results of patients with melanoma), not only about the monotherapy configuration but also regarding association/succession between distinct therapeutic procedures. As an example, targeted therapy with BRAF inhibitors proved to be effective in advanced BRAF-mutant melanoma. However, such treatments with BRAF inhibitors lead to therapy resistance in half of patients after approximately 6 months. Even if most benign nevi incorporate oncogenic BRAF mutations, they rarely become melanoma; therefore, targeted therapy with BRAF inhibitors should be viewed as an incomplete or perfectible therapy. Another example is related to the administration of immune checkpoint inhibitors/ICIs (anti-CTLA-4 antibodies, anti-PD-1/PD-L1 antibodies), which are successfully used in metastatic melanoma. It is currently believed that CTLA-4 and PD-1 blockade would favor a strong immune response against cancer cells. The main side effects of ICIs are represented by the development of immune-related adverse events, which in some cases can be lethal. These ICI side effects would thus be not only therapeutically counterproductive but also potentially dangerous. Surprisingly, a subset of immune-related adverse events (especially autoimmune toxicity) seems to be clearly correlated

with better therapeutic results, perhaps due to an additional therapeutic effect (currently insufficiently studied/exploited). Contrary to the classical approach of cancer (considered until now an uncontrolled division of cells), a very recent and comprehensive theory describes malignancy as a supracellular disease. Cancerous disease would therefore be a disturbed supracellular process (embryogenesis, growth, development, regeneration, etc.), which imposes/coordinates an increased rhythm of cell division, angiogenesis, immunosuppression, etc. Melanoma is presented from such a supracellular perspective to be able to explain the beneficial role of autoimmunity in cancer (autoimmune abortion/rejection of the melanoma-embryo phenotype) and to create premises to better optimize the newly emerging therapeutic options. Finally, it is suggested that the supracellular evolution of malignancy implies complex supracellular messaging (between the cells and host organism), which would be interfaced especially by the extracellular matrix and noncoding RNA. Therefore, understanding and manipulating supracellular messaging in cancer could open new treatment perspectives in the form of digitized (supracellular) therapy.

Introduction

Melanoma is an aggressive form of cancer that is often encountered in young people and usually has a poor response to classical therapeutic methods. One of the standard methods of diagnosing and treating melanoma is represented by surgical resection (due to its facile accessibility, melanoma is frequently located in the skin), so excision is still widely applied at present for patients with early-stage disease. Except for melanoma in situ, the surgical procedure is generally not enough when it is performed as monotherapy [1], local recurrence, and/or metastases develop in most patients after a variable period of time. For this reason, additional therapeutic methods have been tested in the past with variable results, thus trying to improve the difficult therapeutic management of melanoma patients.

As a result, several procedures were introduced over time in the therapeutic approach of melanoma as adjuvant methods, represented currently by chemotherapy (dacarbazine, temozolomide), electrochemotherapy (combining bleomycin and cisplatin with high-intensity electric pulses), biochemotherapy (the combination of chemotherapy and immunotherapy), immunotherapy (interferon α-2b, peginterferon α-2b, interleukin-2, Treg inhibition, CTLA-4 blockade, PD-1 and PD-L1 blockade, Toll-like receptor agonists, adoptive T cell therapy, and gp100 peptide vaccine), oncolytic virus therapy (talimogene laherparepvec), genetically targeted therapies (BRAF, MEK, CKIT, VEGF, PI3K-AKT-mTOR, cyclin-dependent kinase, and ErbB4 inhibitors), photodynamic therapy, and radiotherapy [2, 3].

The latest and most promising therapeutic agents are currently represented by immune checkpoint inhibitors (ICIs) [4•, 5], targeted therapy [6], and oncolytic viral therapy [7]. Unfortunately, these new therapeutic methods generated not only promising results but also additional concerns related to administration (from monotherapy settings to the mode of associations/successions of distinct therapies) [5, 8]. In addition, ICI administration generates even a therapeutic paradox because the therapeutic benefit is no longer as clearly delineated by the adverse reactions encountered (the risk-benefit concept is unclear in this case). This paradox is a consequence of the fact that better therapeutic outcomes related to ICI administration are in fact significantly correlated with a subset of adverse reactions, represented especially by autoimmune events/toxicity [4•, 9••].

Taking into account the above-described therapeutic procedures, the destruction of cancer cells was the main, if not only, goal in the past [10–12]. Studies and interpretations have therefore been limited until now, being unable to integrate and describe malignancy as a whole. Such a comprehensive approach would be, however, essential to be able to interrelate distinct therapeutic forms currently available, to perfect them to become curable, and finally to obtain good control of residual disease.

This paper presents melanoma from a unitary supracellular perspective (describing the melanoma-embryo phenotype) [13••] and the role of

autoimmunity in melanoma regression. New therapeutic perspectives could be advanced starting from this supracellular model, such as the possibility to repair/reset the supracellular process that is disturbed, to channel it towards the final purpose (implying differentiation), to stop it as it is (in the stage where it is), or to be constrained to cohabitate with the host organism. All these therapeutic approaches involve a new concept represented by supracellular messaging, which would be interfaced by the extracellular matrix [14], specific (noncoding RNA) genes directly related to supracellular processes [15], and other possible but still undescribed signals. This new therapeutic approach based on supracellular messaging should be customized in the future for different cancer forms and according to the supracellular process involved.

Discussion

Cellular carcinogenesis

The core element for studying and interpreting cancerous disease is largely represented at present by the cell. This is a consequence of the fact that malignancy is often characterized by exacerbated cell division, associating invasion and metastasis [16]. Such exacerbated proliferations could be, in some cases, caused by mutations in specific genes that intervene in the process of cellular division (somatic mutation theory). Other authors argue that such mutations would actually occur after the carcinogenesis onset [17]. Another perspective about carcinogenesis is that the cells would actually have no changes in the nucleotide sequence but present an altered expression of the respective genes (due to epigenetic alterations, extracellular matrix, intercellular signals, etc.) [18]. From a historical perspective, the cell would be able to integrate all these (intracellular and extracellular) data, with the resulting effect being a malignant phenotype expressed in the form of uncontrolled cell division [10–12, 19, 20].

Regarding somatic mutation theory, some genes encode instructions necessary for specific cellular tasks [13••], while other genes (related to noncoding RNA) belong to supracellular processes of the body [21, 22]. Entire information regarding human evolution and development must be transmitted through a single cell/zygote, so that all these (cellular and supracellular) data are be packed as DNA/genome and placed at the cellular level [23]. This means that malignancy cannot be investigated only at the cellular level because some genes/mutations could actually belong to complex supracellular processes of the body [21, 22]. As an example relevant to the cancer topic, BRAF gene mutations are associated with human cancers (the B-Raf protein is directly involved in transmitting signals for cell growth), but it does not necessarily apply in the same way in any part (cell) of the body. Thus, the frequency of BRAF mutations widely varies, so it is encountered more than 80% in melanomas and benign nevi and to a lesser extent in other cancers [24].

Other classical theories are represented by the tissue organization field theory [25] and the cancer stem cell theory [26]. Generally, these theories consider cancer to be a relational problem between cells. As an example, kidney development implies a bidirectional interaction between the metanephrogenic diverticulum (generating the collecting system) and the metanephrogenic mesenchyme (generating nephrons). Together, these two distinct tissues are able to generate the kidney entirely; taken separately, neither one of these two distinct tissues is able to go further alone on its developmental lineage [27, 28]. This relational problem between cells is correct (as a supracellular approach) but not

a complete viewpoint in cancer because it ignores not only the complexity of the supracellular process involved but also its bidirectional interaction with the host organism. In support of this, the classical theories (relatively delineated) are, for example, unable to explain the beneficial/therapeutic effect of some autoimmune events on malignant melanoma [13••].

In 1892, cancerous disease was compared by Lobstein and Recamier to the developmental process of the body [29], and carcinogenesis has been assimilated with the embryological reprogramming of cells [30, 31]. The first part (related to embryogenesis as a developmental process) is a correct but incomplete perspective because embryogenesis is not the only supracellular process possible within the body [13••]. The second part is often misinterpreted because embryological reprogramming of a cell usually leads to the idea that cancer would be a cellular problem expressed in the form of uncontrolled division of the resulting cells [10–12, 19, 20]. In fact, cancerous disease should be not limited to the cellular level because this affection incorporates clear supracellular participation. In support of this, the extracellular matrix, for example (that is part of supracellular processes), directly contributes to the expression and evolution of malignant phenotypes. Thus, the extracellular matrix is able to stimulate cancer progression [32] or, conversely, is able to abolish the malignant phenotype of metastatic melanoma cells (which revert to the neural crest cell-like phenotype when placed in the embryonic microenvironment) [33–35].

Supracellular processes, phenotype expression, and supracellular messaging

Contrary to the widely accepted historical perspective suggesting that cancer is an uncontrolled division of cells [10–12, 19, 20], a very recent theory argues that exacerbated cell division in cancer would be, in fact, a very controllable and responsive cellular event to supracellular processes/messaging of the body [13••].

From a structural and functional perspective, the deployment of supracellular processes (regeneration, growth, development, embryogenesis, etc.) implies the participation of simplistic structures (such as cells) performing simplistic functions (division, angiogenesis, metabolic pathways, etc.). On the one hand, the supracellular processes should exert a form of control over the cells/simplistic functions involved. On the other hand, the supracellular process could interact constantly and bidirectionally with the host organism to be able to adapt/adjust its control (of the cells and simplistic functions) to the general or local need of the organism. When such a supracellular process is disturbed, a supracellular/systemic disease could be generated, manifested through a specific phenotype (exacerbated cell division, angiogenesis, immunosuppression, etc.) that could be inappropriate (if not detrimental) to the real needs of the body [13••].

The most correct and comprehensive perspective about cancer is therefore represented by the concept of a disturbed supracellular process, which is expressed in the form of a malignant phenotype. The diversity of supracellular processes that could be involved (growth, development, regeneration, embryogenesis, etc.) is able to explain the wide variation existing between different cancer forms and sometimes even within the same cancer. As an example, melanoma cells generally originate from melanocytes. However, superficial

spreading melanoma (related perhaps to embryogenesis) responds satisfactorily to ICI therapy [5], while acral lentiginous melanoma (related perhaps to regeneration due to its localization on the palms, soles, oral mucosa, etc.) presents a poor response to ICI administration [36].

From an informational perspective, the genome incorporates the entire genetic code/data of the organism. This means that the genome provides data not only for specific cellular tasks (especially through protein-coding genes) [13••, 23] but also for supracellular processes of the body. Such supracellular data could be coded by specific DNA sequences related to noncoding RNAs (not translated into proteins). Thus, recent studies have shown that different types of noncoding RNAs (long, micro, circular, small, etc.) intervene as regulators in multiple supracellular processes, such as embryogenesis, regeneration, growth and development, differentiation, metabolic processes, angiogenesis, and immune homeostasis [21, 22, 37–41].

Intervening as regulators of supracellular processes/messaging, noncoding RNAs are implicitly involved in several diseases, including cancer. Thus, noncoding RNAs are involved in the expression of multiple aspects of the malignant phenotype, such as cell proliferation, tumor growth, invasion, migration, and metastasis. [42–44]. For this reason, several studies have been designed to find compounds able to interfere with noncoding RNAs and thus able to interfere with the supracellular evolution of malignancy. For example, the downregulation of noncoding RNA-H_{19} inhibits melanoma cell growth, invasion, and migration, induces G_0/G_1 arrest of the cells and apoptosis, and reverses epithelial-mesenchymal transition in melanoma cell lines [45]. In a similar way, the downregulation of noncoding RNA miR-301b led to a significant inhibition of growth and apoptosis induction in melanoma cells [46].

Melanoma-embryo phenotype

Melanoma cells usually originate from melanocytes, which are derived from neural crest progenitor cells. Recent studies have found that melanoma cells are able, for example, to perform the neural crest stem cell transcriptional program (a supracellular program related to embryogenesis), which ensures not only disease progression but also minimal residual disease after therapy [24, 26, 47]. Sox10 and Rac1 genes intervene in neural crest development; interference with these important genes should be able to prevent melanoma formation [26]. In addition, Nodal signaling (an essential supracellular morphogen of early embryonic axis patterning) promotes not only embryogenesis but also melanoma progression (not encountered in normal skin). Inhibition of Nodal signaling is able to inhibit melanoma evolution (cell invasiveness, colony formation, tumorigenicity) until a total reversion of the melanoma phenotype towards a melanocytic phenotype [48, 49].

In support of the melanoma-embryo phenotype, the literature data describe multiple similarities between embryo development and melanoma. Thus, several embryonic genes, epigenetic regulation, protein profiles, and signaling pathways are re-expressed in melanoma cells [50–52]. The local invasion and metastatic capacity of melanoma is closely related to the expression of a trophoblastic/gestational factor (melanoma cell adhesion molecule), which physiologically intervenes in normal adhesion of the placenta [53]. Immunological tolerance of melanoma is constantly maintained by several

immunosuppressive factors (5T4 oncofetal antigen, nonclassical HLA-G class I antigen, etc.) [54]. Such factors are rarely expressed in normal adult tissues [55] and are usually expressed only during gestation by human trophoblasts to induce immunosuppression and thus immunologic tolerance of the fetus (which in fact is a semiallograft) [53–55].

Benefiting by the possibility of multiple developmental lineages (characteristic embryogenesis), melanoma cells are able to engage in several evolutive phenotypes, such as carcinomas, sarcomas, lymphomas, and germ cell tumors. The differentiation process to nonmelanocytic structures has also been described (smooth muscle, myofibroblastic, osteocartilaginous, etc.) [56, 57]. Moreover, cloning a blastocyst from a RAS-inducible melanoma nucleus generates embryonic stem cells, which proved to be able to differentiate into multiple cell types in vivo (melanocytes, fibroblasts, lymphocytes, etc.) [58].

The role of autoimmunity in melanoma regression

Mimicking embryo development, the melanoma-embryo phenotype exposes and releases natural trophoblastic antigens, which exert physiologic gestational immunosuppression on the host organism. This natural gestational immunosuppression favors melanoma tolerance and development; therefore, melanoma is one of the most frequent malignancies encountered in pregnancy [59]. Conversely, histopathological reports show that spontaneous regression of melanoma implies the absence of immunosuppression in areas of regression. The absence of immunosuppression could be due to specific autoantibodies that act by blocking immunosuppressive natural gestational antigens [60]. For this reason, spontaneous regression in melanoma was suspected to be the consequence of a strong autoimmune reaction (autoantibodies directed against the natural gestational immunosuppressive antigens) [61, 62]. Hostile gestational factors (including autoantibodies against gestational immunosuppressive antigens) are more probable in men than in women; therefore, spontaneous regression of melanoma is reported more frequently in males, with a ratio of 2.7:1 compared to women [63].

People affected by vitiligo (autoimmune reactions destroying melanocytes) seem to have a decreased risk of developing melanoma [64], while for melanoma patients, vitiligo appears to be a positive prognostic factor [65], which is associated with spontaneous regression of melanoma [65, 66]. Similarly, spontaneous autoimmunity is a good prognostic factor for advanced melanoma [66], and several autoimmune diseases are associated with (partial or complete) melanoma regression [67].

In stage III–IV melanoma patients receiving immunotherapy, vitiligo is associated with better survival [68]. For immune checkpoint inhibitors/ICIs, higher immune-related adverse events (especially autoimmune toxicity) are significantly correlated with better therapeutic outcomes [4•, 8, 9••, 67, 69]. When ICI-related autoimmune events are powerful and extensive, the probability of developing antibodies against natural gestational immunosuppressive antigens should theoretically increase. This could be the case/subgroup of melanoma patients responding favorably to ICI administration. When autoimmune reactions induced by ICIs would be weak or absent, the natural/gestational immunosuppressive antigens would not be interfered with by autoimmune antibodies, which means that the phenomenon of immune escape

would continue to persist, further favoring the evolution of melanoma. This could be the case/subgroup of melanoma patients with unsatisfactory responses to ICI administration.

In support of this entity of the melanoma-embryo phenotype, it is interesting to note that vitiligo (involving specific autoimmune reactions) seems to be associated not only with spontaneous regression of melanoma [65, 66] but also with an increased risk of spontaneous abortion [70]. A similar phenomenon is observed for ICIs associated with the rejection/abortion not only of melanoma but also of pregnancy. Higher levels of soluble immunosuppressive antigens PD-L1/sPD-L1 have been described in tumor patients compared with healthy individuals (ensuring the immunologic tolerance of cancer) [71, 72]. However, these immune checkpoint proteins (PD-1/PD-L1, CTLA-4) also ensure embryo-fetal immunologic tolerance. For this reason, the use of ICIs in pregnancy (anti-PD-1/PD-L1) predisposes patients to a high risk of spontaneous abortion [73], while in animal studies, the administration of anti-PD-1/PDL1 significantly increased the risk of spontaneous abortions [74, 75]. In a similar way, CTLA4 intervenes in materno-fetal tolerance; interestingly, CTLA4 serum levels are severely reduced in women with idiopathic recurrent miscarriages compared with control women [76, 77].

As a preliminary conclusion, a good therapeutic response of melanoma to ICI administration would imply an autoimmune abolishment of gestational immunosuppression, namely, an autoimmune rejection of the melanoma-embryo phenotype.

Immune checkpoint inhibitors as monotherapy or in association

ICIs are antibodies against key (checkpoint) immunological proteins (CTLA-4, PD-1, and PD-L1), and currently, ICIs are standard therapeutic options for advanced melanoma. Such ICIs, such as ipilimumab (in 2011) and pembrolizumab and nivolumab (in 2014), have been approved by the FDA for the therapeutic approach of metastatic melanoma. As monotherapy, anti-PD-L1 antibodies induce a positive response to approximately 26–32% of patients [78, 79], while anti-PD-L1 antibodies in association with anti-CTLA-4 antibodies induce a positive response to approximately 60% of patients [80]. Such studies combining CTLA-4 inhibitors with PD-1 inhibitors have led to better therapeutic results in melanoma but have been associated with significantly increased immune-related adverse events [80, 81]. Several studies have shown that such higher immune-related adverse events (especially autoimmune toxicity) are clearly correlated with a higher clinical benefit [4•, 8, 9••, 67, 69].

As a consequence, there is currently a real dilemma about the use of ICIs in malignant melanoma, which can be framed between two extremes [5]. The first extreme is represented by authors who sustain the administration of ICIs with caution (low doses and/or in monotherapy) to minimize the associated adverse effects. This attitude would be necessary because only a subgroup of patients responded favorably to ICI administration, and from responding patients, only a fraction presented long-lasting results. Accordingly, several authors argued that it would require finding reliable biomarkers that could help identify (before therapy) not only the subgroup of patients who would benefit from ICIs but also the primary resistant patients to ICIs (to avoid adverse events to

primary resistant patients) [82].

At the opposite end, there are authors who start from the observation that melanoma is, however, a life-threatening disease and therefore promote complex therapeutic approaches (implying drug associations) that lead to better therapeutic results (but lead to higher adverse events, as presented above). Some investigations went further on this perspective, performing associations not only between different ICI compounds (anti-CTLA-4 antibodies, plus anti-PD-1 antibodies), but they also tested the association between ICIs (for metastases) and the oncolytic virus talimogene laherparepvec (for a local effect), an association that proved synergistic efficacy to patients with unresectable melanoma [83–85]. Triple therapy combining anti-CTLA4 with anti-PD-1/anti-PD-L1 and radiation proved to induce even more profound tumor regression and survival [86].

Specific, nonspecific, and autoimmune adverse events in melanoma

The mechanism of action of ICIs is not yet fully understood [87]. To understand the association between distinct ICI compounds, the association between ICI compounds and other therapeutic forms, and a possible additional therapeutic benefit of autoimmune adverse events, it is necessary to clarify the mechanism of ICI action. Immune checkpoint proteins (CTLA-4, PD-1, and PD-L1) play a downregulatory role over the immune system, suppressing immune responses and inflammatory activity associated with T cells. By decreasing immunologic reactivity, immune checkpoint proteins intervene not only by promoting self-tolerance but also by preventing the immune system from killing cancer cells. Antibodies directed against these immune checkpoint proteins (such as ICIs) directly interfere with the phenomenon of immune downregulation, leading to an opposite effect, namely, increasing the immunologic reactivity of the organism [78–80].

Generally, the therapeutic response of some melanoma patients to ICIs administration is currently considered a consequence of the increased immunological reactivity of the organism [87]. ICIs administration would increase the specific and nonspecific immune mechanisms that intervene for the recognition/destruction of tumoral cells. The nonspecific immune response could be so strong in some patients that it destroys not only the tumoral tissue but also normal tissues of the body (toxic epidermal necrolysis, cardiac or renal injuries, diabetes, etc.), finally leading to several autoimmune reactions described as immune-driven toxicity profiles [73, 88, 89]. Accordingly, the therapeutic approach of melanoma could imply three different types of immunologic responses: specific, nonspecific, and autoimmune reactions.

Regarding the specific anti-tumoral immune response in melanoma, the oncolytic virotherapy with talimogene laherparepvec is able, for example, to induce the direct destruction of tumoral cells, thus facilitating the exposure of tumor antigens and, therefore, the genesis of a strong specific immunological response (until total local regression of the tumor). Unfortunately, talimogene laherparepvec does not appear to have an obvious effect on metastasis. Adding ICIs to talimogene laherparepvec leads to a synergistic action, perhaps due to nonspecific immunity induced by ICIs, which would be able to eliminate metastasis [83–85]. This synergistic action suggests that the specific immunity induced by ICIs could actually be poor. In support of this idea, the

administration of ICIs as monotherapy induces a positive response in fewer patients (than combined with talimogene laherparepvec) and, in patients that respond to ICIs, long-lasting results are found only in a small percentage (poor memory, low specific immunity) [78, 79, 87].

However, higher immune-related adverse events related to ICIs (especially autoimmune toxicity) are clearly correlated with better clinical outcomes [4•, 8, 9••, 67, 69, 88, 89], most likely due to the autoimmune abolishment of natural gestational immunosuppression. In other words, the general mechanisms of ICI action would consist of the induction of nonspecific immunity plus nonspecific autoimmunity, while therapeutic action would be represented by the induction of nonspecific immunity plus specific anti-gestational autoimmunity. This specific anti-gestational autoimmunity would be accidental/aleatory (may result or not from ICI administration), a phenomenon that could explain why only a subgroup of melanoma patients respond to ICI administration.

Possible emerging therapies

Immune checkpoint inhibitors present a core immunologic action. Accordingly, the therapeutic approach of melanoma using ICIs should be revisited/improved, reducing the spectrum of autoimmune reactions induced, if possible only to those autoimmune reactions capable of interrupting gestational immunosuppression (including, for example, but not necessarily limited to, 5T4 oncofetal antigen, HLA-G antigen, etc.) [13••, 55, 62, 90, 91]. In this way, many undesirable side effects could be avoided, and therapeutic specificity and sensitivity would be expected to increase. Compounds discontinuing the process of (gestational) immunosuppression in association with talimogene laherparepvec (for specific immunity) could represent an interesting association.

From a cellular perspective, it is relatively unexplainable how the body (stimulated by ICIs) would be able to completely eliminate melanoma cells (including metastases), but the same organism/immunologic system would be unable to keep residual cells/disease under control [92]. In a supracellular approach, residual disease could be better controlled by associating multiple synergic factors (signals) that are able to induce/maintain a hostile environment for the development of the melanoma-embryo phenotype. A possible example could be represented by the administration of antibodies blocking gestational immunosuppression in association with hormonal compounds (demonstrated to be linked to melanoma evolution) and embryotoxic compounds. Propranolol proved to have embryotoxic potency, inhibiting the growth of the placenta and embryo. Literature data show that propranolol not only inhibits melanoma growth but also significantly limits melanoma recurrence, with an approximately 80% risk reduction [93].

Several studies show (according to electron microscopy) that spontaneous regression in melanoma implies, in addition to autoimmune reactions, specific signals that conduct cells towards apoptosis [94]. In support of these supracellular signals, the process of communication between cells, for example, seems to be essential for both cancer progression and embryological development [13••, 24, 26]. As an example, the Nodal signaling pathway intervenes in differentiation during early embryonic axis patterning. It is absent in normal skin but present in human melanoma metastatic tumors, stimulating

proliferation and invasion. By inhibiting Nodal signals, the aggressiveness of the melanoma phenotype decreases (invasiveness, colony formation, and tumorigenicity) and is even able to promote the reversion of the melanoma phenotype towards a melanocytic phenotype in some cells [48, 49].

Not all cells of a melanoma are stem cells. However, literature data show that it is possible to transform cancer cells (which are not stem cells) into cancer stem cells (using complex messages). After this, the resulting cancer stem cells could be directed towards differentiation or, conversely, be channeled towards apoptosis [95, 96].

The transcription of AP-1 factor $FOSL_1$ leads to melanocyte reprogramming and transformation. This means that the prevention of melanoma should also be taken into account in the future, especially for people presenting predisposing conditions such as dysplastic nevi [97].

Limiting the spectrum of autoimmune adverse events of ICIs

The spectrum of autoimmune reactions induced by ICIs should be restricted to only those autoimmune mechanisms (related to gestational autoimmunity) suspected to induce an additional therapeutic effect. Treatment specificity and efficiency should be thus expected to increase, while the unnecessary autoimmune reactions would be avoided leading to better quality of life. See explanations and an example below.

The embryo inherits genes from both parents, so that it is perceived as a hemi-allograft by the immune system of the pregnant woman. Even if the embryo contains foreign antigens from the father, it is however tolerated by the mother's body, due to gestational immunosuppression which is present during the entire pregnancy. In normal pregnant women, the gestational immunosuppression is induced by natural immunosuppressive antigens like HLA-G antigen, oncofetal antigens, etc. This means that the gestational immunosuppression acts as a natural immunological mechanism, which is very important for the embryo tolerance and pregnancy evolution (namely for the mother to be able to tolerate the hemi-allograft embryo) [62].

Women diagnosed with a history of immunologic abortions presents a low tolerance for the embryo, due to absence of gestational immunosuppression. Such women with history of immunologic abortions present specific autoantibodies in blood, which block the natural immunosuppressive antigens (HLA-G antigen, oncofetal antigens) and thus disrupt the gestational immunosuppression. In fact, these women present a larger spectrum of autoimmune reactions, including not only autoantibodies against gestational immunosuppression but also anti-thyroid autoantibodies, anti-nuclear autoantibodies, vitiligo, etc. Low doses of intravenous immunoglobulin proved to be beneficial for women with immunologic abortions, leading to successful pregnancy evolution [98, 99].

Autoantibodies against gestational immunosuppression are therefore expected to be present in blood of women with history of immunologic abortions. Such autoantibodies or blood could be transferred/transfused to animals or humans with melanoma (respecting the compatibility procedures), in order to verify if these autoantibodies that disrupt the gestational tolerance/immunosuppression are also able to disrupt the melanoma associated tolerance/immunosuppression. If a complete and stable regression of melanoma is obtained after the blood transfusion, then these patients should be further

investigated to identify in detail compounds (antibodies, antigens, lymphocytes) involved in "gestational immunosuppression." Such compounds could be synthetized afterwards (as monoclonal antibodies, etc.) and used to other melanoma patients, to induce a very specific and limited autoimmunity (able to remove melanoma tolerance/immunosuppression).

It would be interesting to know what happens when blood is transfused from patients with spontaneous regressions of melanoma (or from responding subjects to ICIs administration) to subjects with unfavorable evolution of melanoma, and whether this form of autoimmune-based therapy could be useful to other form of cancers, too.

Conclusions

Several factors (cellular dysfunction, genetic mutation, epigenetic regulation, cell-cell interaction, tissue organization, etc.) proved to contribute, to a variable degree, to the genesis of malignant melanoma. In fact, all these factors lead to a common/synergic effect, represented by the disruption of a supracellular process (regeneration, growth, development, embryogenesis, etc.). The disturbed supracellular process is often expressed in the form of a malignant phenotype, implying exacerbated cell division, angiogenesis, metabolic and immunologic events, etc. [13••, 62]. Such a supracellular process is therefore able to explain the existing link between the documented carcinogenetic factors and the metabolic/immunologic targeted therapies developed until now.

Malignancy has benefited for a long time by conventional therapies, such as surgery, chemotherapy, radiation therapy, and immunotherapy. The current conventional therapies (aimed to reduce/eliminate cancer cells) should be completed in the near future by informational therapies. In support of this, the newly emerging targeted therapies (BRAF inhibitors, etc.) are in fact founded on an informational/genetic perspective. Moreover, the developmental theory regarding malignancy also implies an informational perspective, represented by informational reprogramming of the embryological process.

From a physiological perspective, normal embryogenesis is a supracellular process that involves not only the zygote but also the mother/uterus that hosts it. This means that it is incorrect to discuss the complex process of embryogenesis while taking into consideration only the cell/zygote. In support of this supracellular approach, when a cell from a two-cell embryo is removed, the remaining cell will generate a complete embryo (not half of the embryo), meaning that embryogenesis would be an integrated process to the supracellular level [100].

The vast noncoding genome represents more than 98% of the entire human genome. Until recently, noncoding RNA was considered junk/dark RNA matter. Recent data suggest that many noncoding RNAs could be, in fact, related to supracellular processes and/or ancestral data, which have not yet been investigated.

The supracellular perspective presented here implies an informational approach that can offer a better understanding of cancer biology, create premises for customized associations between existing therapeutic options (depending on the supracellular process involved), and finally open new perspectives related to the therapeutic approach of cancer through supracellular (digitized)

messaging. Supracellular messaging (between the supracellular process and host organism) should be differentiated by intercellular messaging (between the cells) and could serve in the future as a communication/therapeutic channel towards the melanoma-embryo phenotype.

Compliance with Ethical Standards

Conflict of Interest
Ion G. Motofei declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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