New Perspectives to Improve the MHC-I Unrestricted Immune Mechanisms against Malignant Tumors

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Abstract

Since malignant tumors parallel with their progression can lose their sensitivity against the MHC-I restricted T lymphocytes because of their escape in tumor antigen presenting, we need immunomodulators which are able to activate MHC-I unrestricted tumoricidal mechanisms of innate immune system. In contrast to the adaptive system, the innate immune cells have regularly a basic activity (priming) which can determine their function ability and render possible a polarity similar to neuroendocrine system. Namely, innate immune cells are committed in two directions. Type-1 cells involve tumoricidal cascade mechanisms which activate the MHC-I unrestricted killer cells (such as NK-cells) and Type-2 cells activate cell proliferation by production of Growth Factors (GFs), affect chronic inflammation, stimulate the angiogenesis and inhibit the type-1 system. As shown in this paper the activity of type 1 cells is down regulated parallel with the tumor progression and available information suggest a regular tumor-induced dominance of type-2 cells. Immunomodulators must improve this disturbed balance. Type-1 natural cells can be activated only via stimulation of phagocytic cells by PAMP like structures which have always a natural origin and the chemistry is not able to produce them. In the tumoricidal activity of MHC-I unrestricted killer cells the expression of NKG2D receptors and the expression of their stress related ligands (MICA/B, UBPL1-3) have pivotal regulatory role generating the kill signal. The aim of this review paper to support hypotheses as to whether an increase in expression of KAR on MHC-I unrestricted killer cells by evidence based plant immunomodulators and parallel stimulating the expression of stress related ligands on tumor cells by GFR inhibitors or cytostatic drugs (such as Gemcitabin) can result in clinical benefits. Case reports using standardized Rice Bran Arabinoxylan Concentrate (Biobran/MGN-3) in combination with GFR inhibitors or Gemcitabin show astonishing clinical responses. Unfortunately, in spite of clinical and immunological evidences this plant immunomodulator is registered only as food supplements and a further research of these hypotheses is therefore hindered.

Quo Vadis Tumor Immunology? Several Exciting Problems of Tumor Defence and Therapeutic Efforts to Find a Solution

Non-reversible and non-repairable tumor induced escape mechanisms from the effect of the highest developed T lymphocytes

As it is well known, B and T lymphocytes in adoptive immune system are operating on the top of the evolution with their very high (10^9 and 10^{15}) specificity and diversity. It is in contrast for the first defence responsible

innate immune system which using Pattern Recognition Receptors (PRR) recognize only Pathogenic Associated Molecular Pattern (PAMP) configurations on surface of microbes and later during its further cascade-like activation their cells react with stress related molecules on membrane of pathologic altered cells. Innate immune cells have a rather limited specificity and diversity. Consequently, during the last twenty years it was always an old dream in tumor immunology to overcome the tumor disease by a regularly activation of adoptive immune system. However, it is also well known that B lymphocytes and by them produced antibodies in a very small degree take part in tumor defence supporting only the binding between effector and tumor cells. In contrast to B cells, the highly specific T lymphocytes (with 10^{15} different specific receptors) undoubtedly take part in the immune surveillance against tumor disease in healthy organisms. Unfortunately, later parallel with the progression of tumor disease T cells lose their efficacy against tumor cells in consequence of escape mechanisms which are not repairable and reversible [1,2]. Among these escape mechanisms the most important one is the loss of MHC-I antigens on tumor cells which are essential for the presentation of tumor associated antigens for cytotoxic T lymphocytes [3]. As shown in the Figure 1, it is well known that in all tumor and healthy cells both self and non-self (such as tumor associated) proteins are regularly broken down in proteasomes with a very high (two million/second) velocity. The generated peptide fragments are presented for CD8 cytotoxic T lymphocytes using MHC-I antigens as presentation molecules which are also regularly produced in the endoplasmic reticulum with a high velocity. The products of presented self-proteins are ignored by T cells because of the negative selection in their development [3]. Tumor cells can be attacked by T cells only in the case if the (in proteasomes generated) products from tumor associated antigens are presented on cell membrane by MHC-I antigens. Unfortunately, there are growing evidence that tumor cells parallel with their progression can lose their capacity to produce sufficient number of MHC-I molecules as a consequence of the escape mechanisms resulting in their hypo-responsiveness to cytotoxic T cells which is not repairable and reversible [4,5].
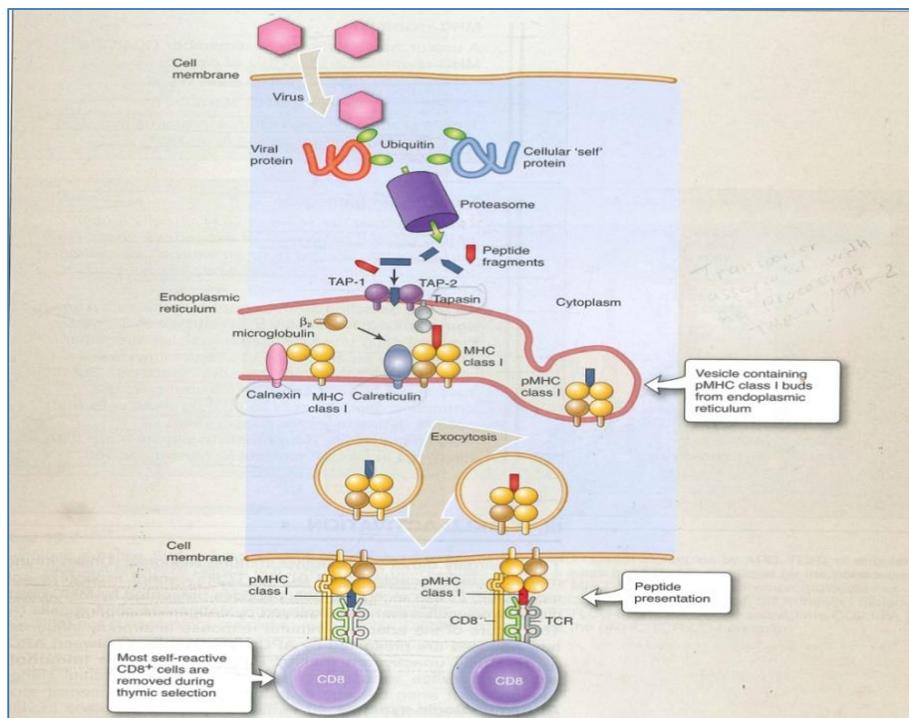
Figure 1: T lymphocyte mediated tumor killing. Virus infected and tumor cells are able to produce non-self-proteins which together with self-proteins are regularly broken down in proteasomes. Then the generated peptide fragments are with a high velocity presented for the CD8 cytotoxic lymphocytes using HLA-I antigens which are regularly produced in endoplasmic reticulum. Tumor cells parallel with their progression begin to produce only an insufficient number and quality of these HLA-I presentation molecules and these alterations are not repairable and reversible. Consequently, the MHC unrestricted immune mechanisms must take over the antitumor functions from the adoptive immune system [Illustration from Hyde M (ed): Immunology 2013 (4)].

Growing attention is focusing on the MHC-I unrestricted innate immune mechanisms

If the tumor cells lose their MHC-I antigens then parallel with their hypo-responsiveness to T lymphocytes there is a growing sensitivity to the MHC-I unrestricted effectors, such as natural killer (NK) cells [4-5]. Since the MHC-I unrestricted effector cells are kept under a strict control by the regulatory mechanisms of innate immune system, it is very important to note that in contrast to adaptive system the innate immune cells have regularly a basic activity (so called priming) which can determine their functions. In addition, similar to neuroendocrine system there is growing evidence that this priming exhibits a polarity. Namely, the innate immune system is committed in two directions.
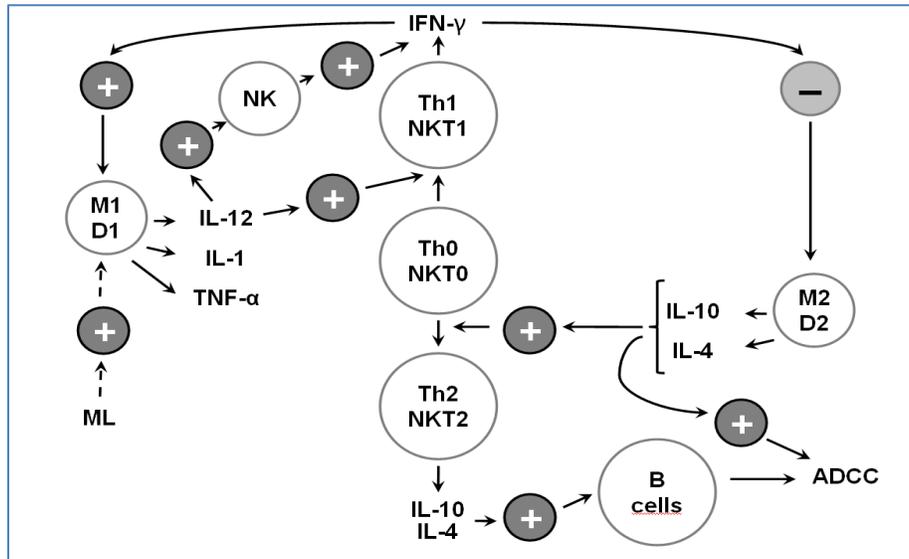

Figure 2: The innate immune system is committed in two directions. M1 and D1 are type-1 macrophages and dentritic cells which take part in the regulation the antitumor killer cells. M2 and D2 are type-2 macrophages and dentritic cells which facilitate the generation of Th2 cells and inhibit the type-1 system. Moderately modified Illustration from JS. Murray [Immunol Today 1998; 19: 157-63].

As shown in Figure 2. the type-1 macrophages (M1) and from monocytes originated type-1 dentritic cells (D1) generate proinflammatory cytokines (only in physiological several pg/ml level), facilitate the production of IL-12, activate cytotoxic effectors, such as NK, gamma-delta T and type-1 NKT1 cells which are potent inhibitors of tumor growth in MHC unrestricted manner [6,7]. However, these type-1 innate immune cells are down regulated in tumor disease (Figures 3A and 3B). Moreover, available information suggests that there is a tumor-induced dominance of type-2 macrophages (M2) and from the plasmocytoid precursors originated type-2 dendritic (D2) cells which generate IL-4 and IL-10 facilitating the generation of Th2 cells and inhibiting the type-1 system. It was also shown that M2 and D2 cells affect chronic inflammation, promote cell proliferation by producing Growth Factors (GFs) and stimulate the angiogenesis. Parallel with the down regulation of type-1 cells, it was also found that tumor patients can have up to 40% type-2 peripheral monocytes in contrast to healthy persons who have only 10% [6,7].

How can we investigate the tumor-induced disturbance of MHC-I unrestricted natural immune mechanisms?

The tumor-induced disturbance of natural immune balance (down regulation of type-1 cells and up regulation of type-2 cells) is hardly detectable by the experienced clinical practise. The most frequent clinical symptoms, such as fatigue syndrome, anxiety or loss of appetite can also be caused by many other reasons. Originally, more than 20 years ago two relatively simply methods were used for investigation of the type-1 natural immune cells:

the phagocytic activity of neutrophil granulocytes and NK activity in peripheral blood of patients. As shown in Figures 3A and 3B, both parameters were shown to be decreased parallel with progression of the tumor disease, [8-9].
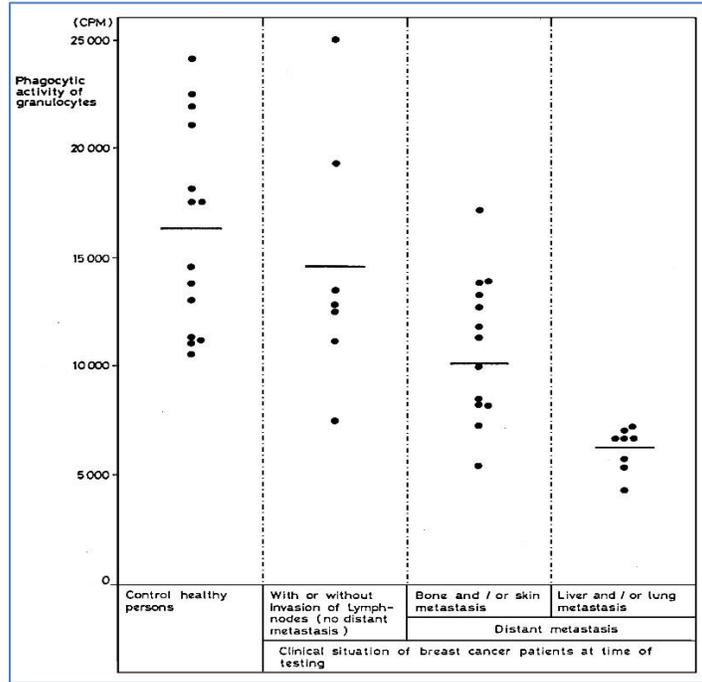
Figure 3A: Phagocytic activity of peripheral neutrophil granulocytes in healthy controls as well as in breast cancer patients without metastases, with bone or skin metastases and with lung or liver metastases. These results can support the tumor-induced down regulation of type-1 innate immune cells which correlates with the progression of the disease [9].
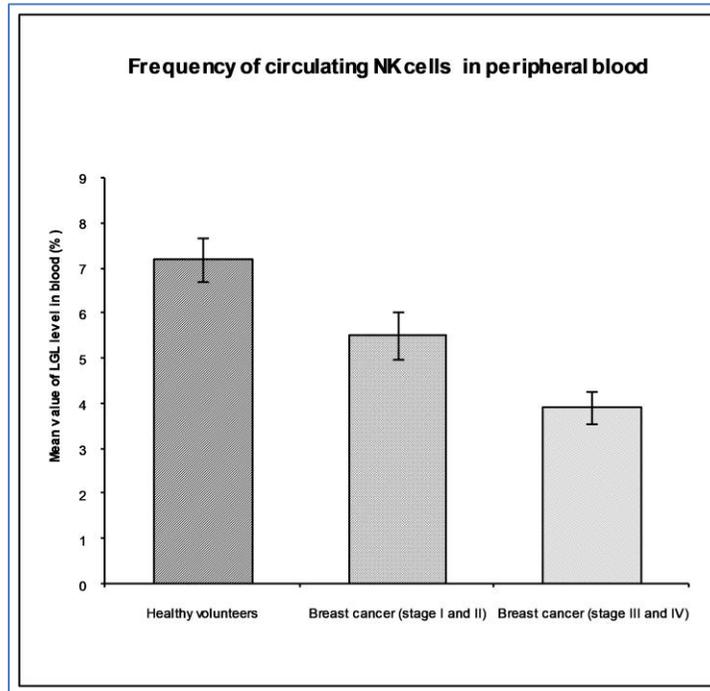
Figure 3B: Similar to phagocytic activity a tumor-induced down regulation was also found if the frequency of circulating NK cells in healthy persons, in breast cancer patients with stage I /II and with stage III/IV of the disease were compared [8].

How could we improve the tumor-induced down regulation of natural MHC-I unrestricted immune mechanisms?

As shown in Fig 3A and 3B, parallel with the progression of the disease both the phagocytic activity and NK level showed a considerable down regulation. It was also remarkable that the degree of reductions of both parameters showed a close relationship with each other suggesting a cascade mechanism of type-1 cellular system [9]. Today it is well known that microorganisms after the binding their PAMP molecules to PRR on surface of phagocytic cells can induce a cascade like activation of type-1 natural immune cells. Therefore, it is not surprising that innumerable attempts were carried out to use bacteria as immunomodulators. However, the most effective pathogenic bacteria can cause undesirable side effects and if we try to diminish their toxicity we can damage the structure of their PAMP molecules. Since PAMP configurations must be rigorously fitted to the configuration of PRR molecules the chemistry is not able to produce them. In spite of the fact that PAMP molecules can never exist in the host they are widely found in the nature. Consequently, growing attention is focusing on the PAMP like molecules with plant origin which in contrast to bacteria have considerably fewer side effects. At the moment, only few amounts of research are available about PAMP-like plant immunomodulators. Unfortunately, the market is full of alternative but poorly investigated and not at least evidence based immunomodulators. In this paper only two evidence based plant immunomodulators will be discussed.

Viscum album agglutinin-I (VAA-I): VAA-I maybe the first PAMP like molecule with plant origin which were subjected to sufficient scientific research. It can be gently isolated from leaves and stem of mistletoe plant [10,11]. VAA-I similar to ricin, abrin (lectin from the red seed of abrus precatorius), modeccin and volkensin, belongs to the type II family of ribosome inactivating proteins (RIP-II) with numerous homologous structures [12,13]. They were isolated from a variety of phylogenetically independent plant species so that the RIPs obviously belong to an old evolutionary development.

The B-chain (34kD) of VAA-I with two PAMP-like structure exhibiting receptors can selectively be bound to terminally alfa-2-6-sialylated gangliosides on phagocytes which can correspond to an appropriate part of PRR. Indeed, using double blind cross over studies it was obvious that VAA-I can activate both the phagocytic activity (after 5h) and NK-functions (after 24h) in peripheral blood of healthy volunteers with a bell-shaped curve of efficacy indicating that VAA-I may be a possible candidate to improve the tumor induced disturbance of natural immune system [14]. Its most effective doses were between 0.5 ng/kg and 1.0 ng/kg observed. Unfortunately, more than twenty years ago from economic reasons was this lectin research stopped and now for clinical use only in term of lectin content standardized mistletoe extracts are available in several countries. (The manufacturer is Hiscia AG, CH-4144 Arlesheim, Switzerland).

Arabinoxylan concentrate from rice bran (BioBran/MGN-3): The most investigated and evidence based plant immunomodulator is an arabinoxylan concentrate from rice bran (RBAC) which is manufactured and supplied in a standardized form as BioBran/MGN-3 by Daiwa Pharmaceutical Co, Ltd, Tokyo, Japan. It is composed of denaturated hemicellulose, which is obtained by rice bran hemicellulose reacting with multiple carbohydrate hydrolyzing enzyme from shiitake mushrooms. BioBran/MGN-3 preparations are standardized for its main chemical component: arabinoxylan with a xylose (in its main chain) and with an arabinose polymer (in its side chains). This plant immunomodulator strongly differ from other plant preparations since the enzymatic fermentation can break down each sort of glycolytic bond except the binding between arabinose and xylose. It results in an arabinoxylan configuration with similar form which exists in the plant retaining its PAMP like properties.

Indeed, this gently by hydrolyzing enzyme isolated RBAC has a similar immunomodulatory effect as VAA-I lectin with PAMP like properties. A great number of publications reports that given in doses between 15 and 45 mg/kg RBAC can activate the type-1 natural effectors, such as phagocytic and NK activities [15-26] and exhibit clinical benefit [27-29]. A double blind randomized clinical trial with liver cancer patients showed that BioBran/MGN-3 given daily with a low dose for 12 months parallel with chemotherapy was able to induce a six-fold increase in the two years survival [27]. In spite of the fact that RBAC is the best evidence based and standardized plant immunomodulator without any side effect, all over the world it is registered as food supplement and not used in oncologic centers. Consequently, its clinical research is regularly hindered.

Ethics Committee mostly refuses the permission for controlled clinical trials with food supplement and only case reports are mainly allowed

The cautious behavior of Ethics Committee and Oncologic Centers with evidence based food supplements is very regrettable since a possible manipulation of the polarity in innate immune system could open new perspectives in the tumor research. Case reports suggest always more hypotheses which can't be further investigated in clinical trials. Since the polarity of neuroendocrine system with the polarity of natural immune system exhibits a close relationship, a great number of preliminary clinical observations become always more exciting.

In the next part of the paper several hypotheses will be presented and discussed which are based on case reports.

Beneficial Clinical Effect with Combinations of Growth Factor Receptor (GFR) Signaling Pathway Inhibitors and Evidence Based Immunomodulators (RBAC): A Hypotheses Based on Case Reports

The central role of NKG2D and its ligands in the regulation of MHC unrestricted Killer mechanisms. Stimulatory effects of GFR inhibitors

The most important and mostly investigated MHC unrestricted killer cells are the NK-cells which have a great number of various receptors on their cell membrane. Among these NK receptors there is a for tumor defence pivotal killing activator receptor (KAR), namely the NKG2D (heterodimer glycoprotein consisting of CD94 homogenous and G2 heterogeneous parts). Their so-called stress-related ligands, such as MHC class-I Chain related A and B (MICA/B) and UL-16 Binding Proteins (ULBP 1-3) are widely expressed on various tumor cells. As it was mentioned above, the loss of MHC-I antigens can decrease the sensitivity of tumor cells against T lymphocytes, but it can increase their sensitivity against NK and other MHC-I unrestricted killer cells (such as type-1 NKT, gamma/delta T and probably several alpha/beta T cells too). Therefore, the regulation of both NKG2D and its stress-related ligands has a crucial importance. As it was mentioned, the dominance of M2 and D2 cells in tumor patients can lead to an enhanced production of growth factors which can contribute not only to the down regulation of the type-1 natural immune cells but they can also diminish the expression of the NKG2D ligands. Indeed, it was shown that Epidermis Growth Factors can inhibit the NK cytotoxicity against cancer cells by down regulating the expression of ULBP 1-2 or MICA and MICB on the tumor cell membrane [30-31]. Therefore, as shown in figure 4, the expression of NKG2D on killer cells and the expression of stress related molecules on the tumor cells can play an important role in the regulation of MHC-I unrestricted natural effector mechanisms.
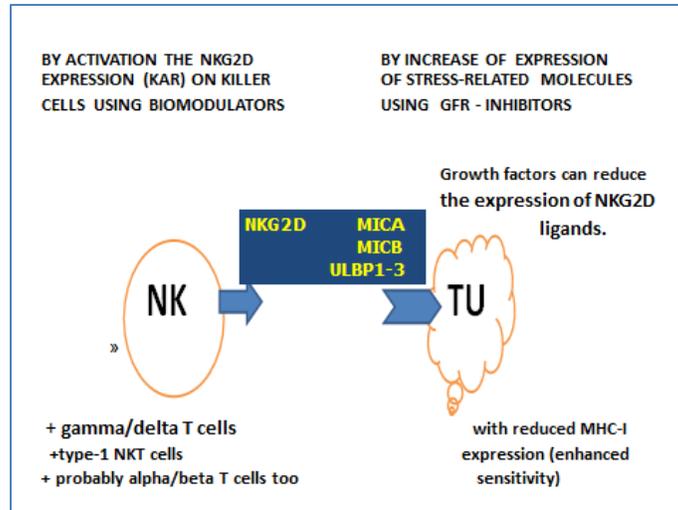
Figure 4: Possible mechanisms to increase the MHC-I unrestricted killer functions.

Case report of a patient with lung adenocarcinoma who were treated with a combination of Erlotinib (GFR-tyrosin-kinase inhibitor) and evidence based immunomodulators (RBAC)

As it was mentioned, the stimulatory effect of GFR signalling pathway inhibitors on the expression of stress-related molecules resulting in an enhanced sensitivity of tumor cells to NK cytotoxicity. Therefore, their combination with evidence based immunomodulators, which can increase the NKG2D expression and the cytotoxicity of NK cells against these by GFR inhibitor sensitized tumor cells, is very promising. Indeed, following case report may support this synergistic effect. A 75 years old patient with inoperable lung adenocarcinoma showed during a chemotherapy with four cycles Carboplatin and Paclitaxel a very rapid progression. The patient was in a terminal state. Therefore, the chemotherapy was stopped and Erlotinb (daily 75mg Tarceva) was started in a combination with standardized (RBAC and VAA-I extract) immunomodulator treatment. As shown in Figure 5, seven months later a nearly complete remission was established by CT and the duration of this remission was longer than three years.
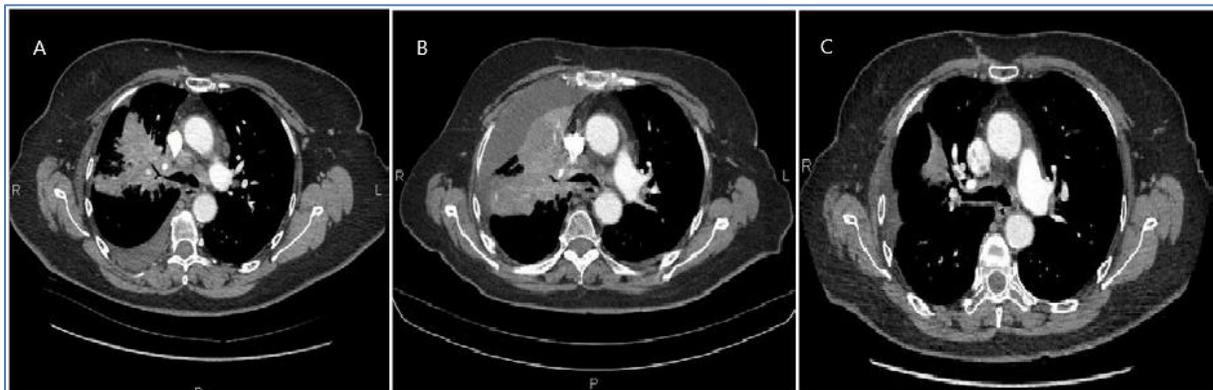

Figure 5: CT investigations of lungs in the patient with inoperable adenocarcinoma which is localized on the boundary of middle and lower right lobes which were accompanied with an extensive atelectasy (A) prior the chemotherapy; (B) after four cycles Carboplatin (110 mg/m^2) and Paclitaxel (90 mg/m^2); (C): seven months after a combinative treatment with Erlotinib (75 mg daily) and standardized plant immunomodulators giving 0.75 ng/kg VAA-I in extract and 45 mg/kg RBAC.

Erlotinib belongs to the first agents to target tyrosine kinase of the EGFR. Clinical trials of patients with advanced non-small-cell lung cancer (NSCLC) who had or had previously been treated with chemotherapy the response rate to EGFR tyrosine kinase inhibitor between 8% and 15% was found [32,33]. Interestingly, in a very large study, in that the median survivals of 1466 patients were compared after chemotherapy (75 mg/m^2 Docetxel every 3

weeks) versus EGFR inhibitor (250 mg/daily Gefitinib), no significant differences were found [34]. Therefore, this beneficial combination of EGFR inhibitors with standardized and evidence based plant immunomodulators is very promising.

Case report of a patient with carcinoma in biliary duct who were treated with a combination of another GFR signaling pathway (MEK/BRAF) inhibitors and of evidence based immunomodulators (RBAC)

Similar to the combination with Erlotinib but maybe it is a more exciting case report in that MEK /BRAF inhibitors were combined with evidence based immunomodulator (BRCA). As it well known, MEK (Mitogen activated Extracellular signal regulation Kinase) inhibitors can down regulate the MAPK (Mitogen Activated Protein Kinase) cascade (RAS / RAF/ MEK / ERK) which plays an important role in the enhanced cell cycle progression and cell migration in tumor patients. In case of BRAF mutations between MEK and BRAF inhibitors exists a synergistic effect. Moreover, similar to erlotinib MEK inhibitor can also up regulate the expression of stress-related molecules (MICA/B, ULBP1-3, see Figure 4). Yang L et al. [35] reported that "the most significant effect of MEK/Erk signaling inhibitors is the recovery of tumor induced decrease of NKG2D ligands (MICA/B and ULBP1-3)." However, in spite of their immune sensitivity enhancing effect, MEK inhibitors alone (without immunomodulator) can induce only a transient clinical remission and a complete remission is rarely observed. Outgrowth of MEK inhibitor resistant clones within progressed tumors appears to be inevitable [36]. (Manufacturers are now considering their further production). Therefore, the astonishing results of following case report, in that MEK inhibitor was combined with high doses of evidence based immunomodulator (RBAC), are very surprising.
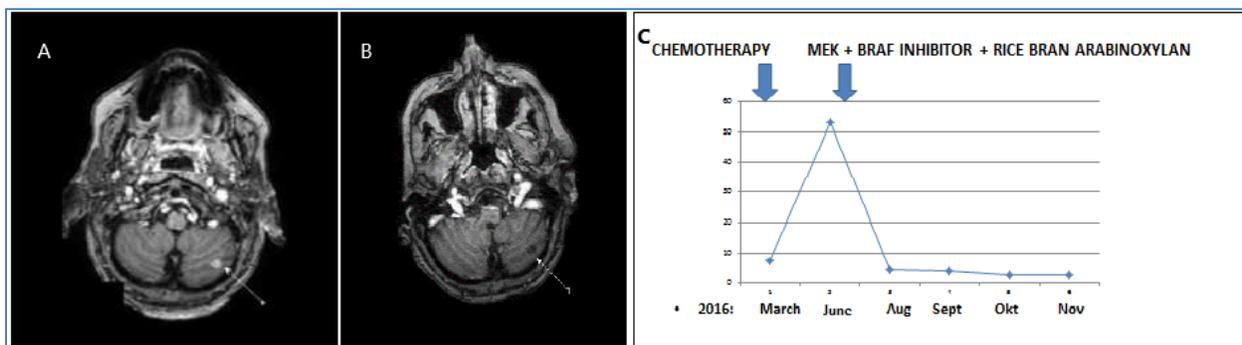
Figure 6: MR investigations of a patient with biliary duct cancer represents a complete remission after a treatment with 1 × 2mg Trametinib and 2 × 150mg dabrafenib combined with 45 mg rice brai arabinoxylan concentrate. Parallel the CEA tumor marker showed also a rapid normalization. **(A)** Prior to therapy with MEK inhibitor and RBAC 45mg/kg; **(B)** 7 months later;**(C)** Rapid decrease of CEA after a combination of MEK inhibitor with RBAC

A 58-year-old patient with inoperable low differentiated adenocarcinoma in biliary duct after 30 GY irradiation and two cycles chemotherapy (Gemcitabine and Cisplatin) a very rapid progression of lung, liver and brain metastases were established by CT and MR investigations. The patient was nearly in terminal state. The chemotherapy was stopped and a treatment with MEK and BRAF inhibitors was started in a combination with daily 45 mg/kg RBAC and after 4 weeks a rapid improvement of her disease was observed. Eight months later nearly complete remissions of all metastases were established by CT and MR. Figure 6 demonstrates complete remission of a brain metastasis in cerebellum and the rapid improvement of her tumor marker.

The astonishing results of these two case reports can suggest the hypothesis that enhancing effect on NKG2D expression by evidence based immunomodulator (RBAC) parallel with an enhancing effect on expression of stress related ligands by Growth Factor receptor signaling pathway inhibitors may result in a synergistic clinical benefit.

Further clinical investigations are necessary to prove this hypothesis but for this aim we need an acceptance for evidence based immunomodulators.

Combination of Cytostatic Therapy with Evidence Based Immunomodulator (RBAC) May Also Open New Perspectives in Tumor Research: A Hypotheses based on Case Reports

Effect of cytostatic therapy (such as Gemcitabin) on the stress related NKG2D ligands (MICA/B, ULBP1-3) on tumor cells

Clinical observations can often suggest a clinical benefit if conventional cytostatic treatment is combined with evidence based and standardized immunomodulator. For example, Bang et al have found in a double-blind clinical trial in that liver cancer patients were treated with and without BRCA parallel conventional chemotherapy that the two years survival was six-fold higher in BRCA group [27]. Consequently, the question arose as to whether several cytostatic drugs can also enhance the expression of NKG2D ligands resulting in enhanced sensitivity to MHC-I unrestricted killer mechanisms. At present not too, much data about it are available. On this occasion the interesting results of Morisaki et al. [37] must be mentioned. These authors investigated the effect of Gemcitabin on MICA/B expression in culture of T24 urothelial cancer cells. 0.1 µg/ml concentration of Gemcitabin was able to induce a more than twice increase in expression of MICA/B on cancer cells. Interestingly higher doses (for example 1 µg/ml) were less effective. Other authors have also established these results [38,39]. It was also shown that the NK sensitivity of T24 urothelial cancer cells with and without IL-2 was also elevated [37]. Clinical case reports can support these in vitro results.

Two case reports in that the combination of Gemcitabin with evidence based immunomodulators (RBCA and VAA-I) results in astonishing clinical responses

A 55 years old breast cancer patient after the chirurgic operations progressive skin metastases are set in on the chest which were resistant against various cytostatic treatments. However, as shown in Figure 7, these skin metastases showed a rapid remission after a treatment with a combination of Gemcitabin and evidence based standardized plant immunomodulators. Parallel with the clinical remission the tumor markers (CEA and CA15-3) are also normalized after six months.
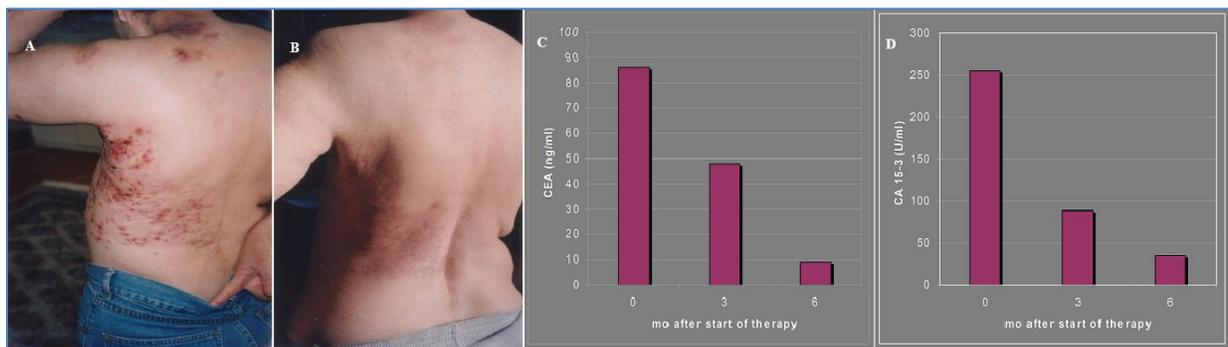
Figure 7: Histological documented skin metastases of a breast cancer patient showed a very rapid remission after a treatment with Gemcitabin and standardized plant immunomodulators. Tumor markers were also normalized after six months. **(A)** Prior to the therapy; **(B)** After six months; **(C)** CEA; **(D)** CA-15-3

In another case report with combination of Gemcitabin and immunomodulator similar astonishing results were observed. A now 48 years old patient with metastatized and in years 2012 and 2014 chirurgical operated bilateral ovarian carcinoma after 16 cycles Taxol and Carboplatin therapy had a local recurrence on the right side which was chirurgic not removed. The chemotherapy with Taxol and Carboplatin was stopped and in January 2016

Gemcitabin in reduced doses was started. Parallel standardized and evidence based plant immunomodulators were also given. As shown in Figure 8, after 14 months a complete remission was established by CT investigation. After 28 treatments the Gemcitabin therapy was stopped and one year later 2 × 400mg several months later 2 × 300mg PARP (Poly-ADP-Ribose-Polymerase) inhibitor was started. Parallel the patient is treated with immunomodulators and until Sept 2018 she is tumor free.
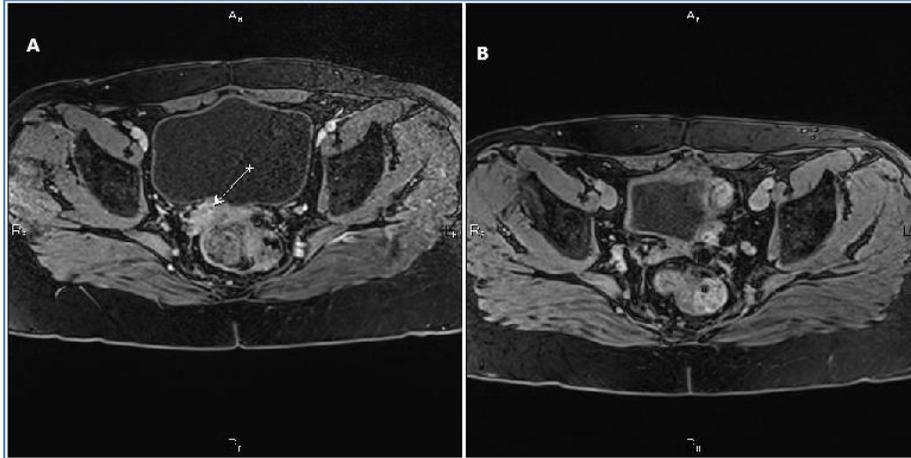

Figure 8: Complete remission of local recurrence of a 2012 and 2014 chirurgic operated ovarian carcinoma patient. After 16 cycles the Taxol and Carboplatin treatment were stopped and in January 2016 a combination of Gemcitabine (given in reduced doses) and plant immunomodulators (lectin and arabinoxylan) was started. **(A)** Prior to the treatment; **(B)** 14 months later

Is the combination of low dose chemotherapy with evidence based immunomodulators also promising?

The effect of lower doses of chemotherapy on the immunoregulation is poorly understood. Preliminary data [40] suggest higher maximum tolerated doses can stronger stimulate the type-2 cells regulating T cells and the suppressor macrophages. This hypothesis seems to be supported with following case report.

A 49-year-old patient had ductal mammary carcinoma [T2 N1 (3/17) Mx], a tumorectomy in January 2010, and subsequently a hormone treatment (Femara) and chemotherapy (six cycles epirubicin and docetaxel) were carried out. In April 2011 multiple hepatic metastases were detected in PET/CT. In December 2011 seven liver metastases were removed by surgery. Six weeks later a considerable progression of hepatic metastases was established in PET/CT. Because of the bad liver functions only a mono-chemotherapy with 60-70% reduced doses (2000 mg later 1500 mg Xeloda/day) was given for 21 day per month. In the same time an immunomodulatory treatment with lectin-standardized immunomodulators (RBAC and VAA-I) was started. In April 2012 a considerable remission of the hepatic metastases (only three small metastases) were detected in CT (Figure 9). From January 2012 until July 2012 the tumor markers decreased: carcinoembryonic antigen (CEA) from 36.1 to 2.95 ng/ml and the tissue polypeptide antigen (TPA) from 232 to 56.3 U/l (Figure 9). A rapid improvement of liver functions was also observed. In August 2012 a nearly complete remission of the hepatic metastases could be established. (The metastases were not measurable in CT). The quality of life was thereafter excellent, the patient has been able to work 100%.
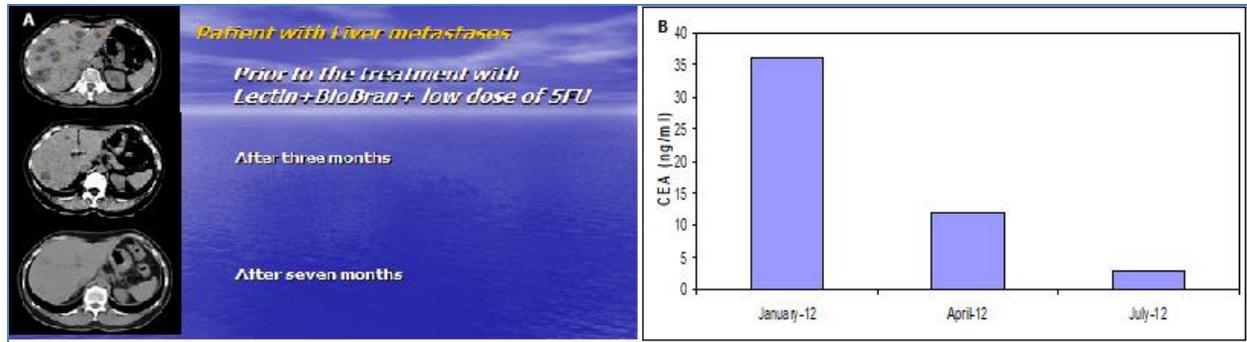
Figure 9: Liver metastases of a breast cancer patient who were treated a with 60 and 70% reduced Xeloda doses in a combination with evidence based plant immunomodulators. **(A)** After seven months the liver metastases were not measurable in CT **(B)** Tumor markers (CEA) are also normalized.

Conclusions

Taken together the above described data and results we can conclude that NKG2D receptor on NK and on other MHC-I unrestricted killer cells and their stess-related ligands on tumor cells are pivotal regulator molecules in the tumor defence.

Our case reports may also support the hypothesis that an activation of killing activator receptors (NKG2D) by evidence based and standardized plant immunomodulators and a parallel stimulation of expression of their ligands (MICA/B and ULBP1-3) with GFR inhibitors or with lower doses of Gemcitabin or of other cytostatic drug can open innovative approach in the tumor therapy.

Rice Bran Arabinoxylan Concentrate (RBAC) which is manufactured with the name of BioBran or MGN-3 is one of the best evidence based and standardized immunomodulator. Unfortunately, because of plant origin BioBran/MGN-3 is registered only as food supplement in the whole world and ignored in oncological centers. Since at present we don't have better evidence based immunomodulators, the further research of above mentioned hypotheses is hindered. What can we do?

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