Article title: The Link between Cancer, Autoimmunity and Diabetes

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ABSTRACT

In cancer, corrupted neoplastic cell successfully evades the immune attack using two main strategies: avoiding the immune recognition and instigating an immunosuppressive tumor microenvironment. Cancer is able to induce immune tolerance and present itself to immune system as normal tissue. There is a defect in immune tolerance: the tolerance is wrongly induced toward cancer. In autoimmune diseases, immune system attacks normal tissue because it fails to recognize its own constituent parts as self. There is a defect in immune tolerance: the tolerance is lost toward normal tissues. In both diseases wrong information in the communication between tissue (neoplastic) cells and immune system is crucial: in cancer, neoplastic cells avoid immune attack, whilst in autoimmune diseases, immune system attacks normal cells. Diabetes mellitus type I and II are associated with an increased risk of developing different types of cancer. Pathogenesis of diabetes mellitus type I and pathogenesis of cancer overlap in genetic, environmental and immunologic factors. Diabetes mellitus type II and obesity can both induce oncogenesis.

INTRODUCTION TO CANCER AND INFLAMMATION

Both autoimmune diseases and cancer stage relates with the functional status of the immune system and circulating levels of cytokines.

Stage I (early onset) is characterized by mild-to-moderate inflammation resulting from recruitment of innate immune cells (for example, myeloid cells) to sites of inflammation. At this stage, inflammation and most tumors are contained within a target organ or diseased (*in situ*) organs.

Stage II (mild course) is characterized with an evidence of an activated adaptive immune system featuring T and B cell proliferation and production of autoantibodies compared with stage I in autoimmune diseases. Tumors are larger than in stage I, but tumor cells remain contained within diseased organs or have started to spread locally into lymph nodes. Tumor-secreted cytokines (GM-CSF, macrophage-CSF, IL-12) can be detected in serum.

Stage III (moderate course or active) is characterized by an intermittent or progressive course that could include

severe episodes of activity. This stage features predominant recruitment, activation, and proliferation of leukocytes (neutrophils, eosinophils, basophils) at sites of inflammation, including single or multiple target organs or tumors. In this stage there is increased tumor burden and metastatic spread into surrounding tissues and distant lymph nodes.

In stage III of autoimmune diseases many patients exhibit comorbid conditions related to advancement of immunopathology (muscle atrophy in rheumatoid arthritis, moderate nephritis in systemic lupus erythematosus).

Stage IV (severe course) indicates end-stage disease. It results in constantly abnormal inflammatory processes associated with severe comorbid conditions and organ failures such as kidney failure in SLE or widespread metastasis for cancer¹.

Primary and metastatic tumors are complex ecosystems composed of neoplastic cells, extracellular matrix (ECM), and accessory non-neoplastic cells, which include resident mesenchymal support cells, endothelial cells, and infiltrated inflammatory immune cells. Cross-talk between cancer cells and accessory cells fuels and shapes tumor development. During tumor formation, the tissue

architecture evolves into a highly specialized microenvironment characterized by a corrupted ECM and chronic inflammation. Cancer-associated inflammation contributes to genomic instability, epigenetic modification, induction of cancer cell proliferation, enhancement of cancer anti-apoptotic pathways, stimulation of angiogenesis, and, eventually, cancer dissemination^{2,3}.

Chronic inflammation is a critical hallmark of cancer, with at least 25% of cancers associated with it⁴⁻⁶.

Possible underlying causes of chronic inflammation are microbial infections, autoimmunity, and immune deregulation.

Examples:

1. Human papilloma viruses (HPVs) induce inflammation and are responsible for 90-100% of all cervical cancers⁷.
2. Chronic infections with *Helicobacter pylori* elevate the risk for gastric cancer⁴.
3. The immune deregulation seen in inflammatory bowel disease increases colorectal cancer incidence⁸.
4. The nonhuman form of sialic acid (N-glycolylneuraminic acid) in red meat can be incorporated into human tissue and recruit inflammatory cells⁹.

5. Tobacco and obesity, both of which induce low-grade inflammation, give rise to elevated risks of cancer¹⁰.

6. Epstein–Barr virus (EBV) infection, malaria, immunodeficiency and spontaneous, somatic mutation can all contribute to the origin and maintenance of Burkitt lymphoma (aggressive B-cell malignancy)¹¹.

7. Systemic lupus erythematosus is associated with an increased risk of developing cervical, lung and breast cancer, as well as Hodgkin and non-Hodgkin lymphoma^{12, 13}.

8. Rheumatoid arthritis is associated with an increased risk of developing lung, breast and ovary cancer, as well as T cell non-Hodgkin lymphoma, follicular lymphoma and diffuse large B cell lymphoma^{12, 13}.

9. Primary Sjögren syndrome is associated with an increased risk of developing oropharyngeal carcinomas and mucosa-associated lymphoid tissue type B cell lymphoma^{13, 14}.

10. Systemic sclerosis is associated with an increased risk of developing lung, skin and esophageal cancer¹³.

11. Wegener granulomatosis is associated with an increased risk of developing urinary bladder cancer¹².

HOW DOES CANCER EVADE THE IMMUNE SYSTEM?

It is currently accepted that an aberrant innate and adaptive immune response contributes to tumorigenesis by selecting aggressive clones, inducing immunosuppression, and stimulating cancer cell proliferation and metastasis¹⁵.

Macrophages are crucial drivers of chronic cancer-associated inflammation. Their involvement has been described in every step of cancer progression, from early neoplastic transformation throughout metastatic progression to therapy resistance¹⁶⁻¹⁸.

In oncological patients and preclinical experimental models, high-grade tumor-associated macrophages (TAMs) correlate with poor prognosis and reduced overall survival^{16, 19}.

TAMs (M2-type, anti-inflammatory, protumorigenic) promote tumor progression in different ways:

- 1) stimulation of angiogenesis and lymphangiogenesis,
- 2) stimulation of both cancer cell proliferation and epithelial-mesenchymal transition,
- 3) limitation of the efficacy of therapies,

- 4) remodeling of the extracellular matrix,
- 5) promoting metastasis,
- 6) and induction of immunosuppression of anti-tumor effector immune cells²⁰⁻²².

High levels of tumor-associated neutrophils (TANs), high levels of neutrophilia, and/or high neutrophil/lymphocyte ratios have been associated with an adverse prognosis in different malignances^{23, 24}.

NK cells have a well-documented anti-tumor effect^{25, 26}. The presence of NK cell infiltration in colorectal and gastric tumors correlates with a favorable outcome^{27, 28}.

A high level of T-cell infiltration in tumors is associated with a favorable prognosis in melanoma, and breast, lung, ovarian, colorectal, renal, prostate and gastric cancer^{17, 29-37}. The presence of tumor-infiltrating CD8⁺ T cells and Th-1 cytokines in tumors correlates with a favorable prognosis in terms of overall survival and a disease-free survival in many malignancies. But, cancer cells exploit the immunosuppressive properties of T cells while impairing the effector functions of anti-tumor T cells, such as their ability to infiltrate tumors and their survival, proliferation, and cytotoxicity³⁸.

Most neoplastic cells expressing highly immunogenic antigens will be recognized and killed by T-cells during the early stages of tumor development³⁹.

The less immunogenic cancer cells escape the immune control of T cells and survive (cancer immune editing)⁴⁰.

The final outcome is that the surviving cancer cells adopt an immune-resistant phenotype.

To conclude, tumor cells evade the immune attack using two main strategies: avoiding the immune recognition and instigating an immunosuppressive tumor microenvironment.

AVOIDANCE OF THE IMMUNE RECOGNITION

Cancer cells may lose the expression of tumor antigens on the cell surface, thus avoiding the recognition by cytotoxic T cells.

Examples:

1. 40% of non-small cell lung cancers hold a loss of heterozygosity in human leukocyte antigens (HLAs), which leads to immune escape by presenting fewer antigens⁴¹.
2. HLA loss has been associated with resistance to T-cell transfer therapy in metastatic colorectal cancer⁴².

3. HLA loss has been associated with poor outcome response to checkpoint blockade immunotherapy in melanoma and lung cancer patients⁴³.

IMMUNOSUPPRESSIVE TUMOR MICROENVIRONMENT

Cancer cell-derived factors instigate an immune-tolerant tumor microenvironment by various mechanisms:

1. Secretion of suppressive molecules such as IL-10, TGF- β , prostaglandin E2 and VEGF⁴⁴⁻⁴⁷.
2. Expression of inhibitory checkpoint molecules such as PD-L1, CTLA-4, and V domain immunoglobulin suppressor of T-cell activation (VISTA)⁴⁸⁻⁵⁰.
3. Induction of the recruitment of TAMs (tumor-associated macrophages), MDSCs (myeloid-derived suppressor cells), and Tregs by tumor-derived chemokines such as CCL2, CSF1, CCL5, CCL22, CXCL5, CXCL8, and CXCL12^{22, 51-53}.

AUTOIMMUNITY

Autoimmunity is the mechanism where an organism fails to recognize its own constituent parts as self, which results in an immune response against its own cells and tissues^{54, 55}.

Mechanisms of autoimmune diseases are:

1. Bypass of helper T-cell tolerance.

Tolerance of CD4⁺ helper T cell may be broken if the helper T cells are bypassed or substituted.

2. Emergence of sequestered antigen.

The induction of tolerance requires interaction between the antigen and the immune system. Any self-antigen that is completely sequestered during development is likely to be viewed as foreign if introduced into circulation.

3. Imbalance of suppressor helper T-cell function.

A loss of suppressor T cell function will contribute to autoimmunity. Excessive T-cell helper function may drive B cells to extremely high levels of autoantibody production.

4. Microbial agents in autoimmunity.

Microbes (bacteria, mycoplasmas, viruses) may trigger autoimmunity. Viral antigens and autoantigens may become associated to form immunogenic units and bypass T-cell tolerance. EBV is polyclonal B-cell mitogen and may induce formation of autoantibodies. Viral infection may result in loss of suppressor T-cell function.

5. Molecular mimicry. Some infectious agents cross react with human tissues and their haptenic determinants. The infectious microorganisms may trigger an antibody

response by presenting the cross reacting haptenic determinants in association with their own carrier to which helper T-cells are not tolerant. The antibody so formed may then damage the tissue that shares cross reacting determinants.

6. Polyclonal lymphocyte activation.

Some microorganisms and their products are capable of causing polyclonal (antigen nonspecific) activation of B cells. Bacterial lipopolysaccharide (endotoxin) can induce mouse lymphocyte to form anti-DNA, antithymocyte and anti-red cell antibodies *in vitro*⁵⁶.

INTRODUCTION TO CANCER AND TYPE I DIABETES

Carstensen and coworkers found in the five-country study (Australia, Denmark, Finland, Scotland and Sweden) that, on average, type 1 diabetes confers an excess incidence of several cancers. In particular, persons with type 1 diabetes had a **higher incidence of cancer of the liver, pancreas, kidney, endometrium and ovary** and a lower incidence of prostate cancer than those in the general population (possibly because of the lower testosterone levels present in men with diabetes). However, similar to the findings for type 2 diabetes, the HRs (hazard ratios) of cancer were highest at time of diabetes diagnosis

and declined over time. They also found an **increased risk of thyroid cancer** in persons with type 1 diabetes compared with the general population, particularly among women^{57, 58}.

OVERLAPPING GENETIC AND IMMUNOLOGIC FACTORS IN DIABETES TYPE I AND CANCER

Type 1 diabetes mellitus (T1DM) represents only around 10% of the diabetes cases worldwide, but occurs with increasing incidence much earlier in life. T1DM results from the autoimmune destruction of β cells of the endocrine pancreas. A small percentage of affected patients (<10%) are classified as type 1B, with no evidence of autoimmunity and the pathogenesis in these cases is considered idiopathic⁵⁹⁻⁶¹.

1. Major histocompatibility complex

More than 90% of the patients with T1DM have either HLA-DR3, **DQB1*0201** (DR3-DQ2) or HLA-DR4, **DQB1*0302** (DR4-DQ8) haplotypes compared to 40% of the healthy individuals. About 30% of the patients have both haplotypes (DR3/4 heterozygotes^{62, 63}). The presence of some DR4 alleles (DRB1*0403, DPB1*0402) reduces the risk of T1DM development even in the presence of DQB1*0302 high-risk allele. The HLA allele DQB1*0602

provides protection against T1DM development^{60, 64, 65}.

Kübler and coworkers conducted a study with a sample of 52 Caucasian patients with primary ovarian carcinoma and 239 female healthy local controls. They observed a significantly increased incidence of the HLA-class II haplotypes DRB1*0301—DQA1*0501--**DQB1*0201** ($p < 0.001$) and DRB1*1001 – DQA1*0101 – DQB1*0501 ($p < 0.001$) in the patients with primary ovarian carcinoma⁶⁶.

Machulla and coworkers found in their study on German patients that the presence of alleles HLA-DRB1*0401, **HLA-DQB1*0302** and HLA-DPB1*0301 was associated with a higher risk for chronic lymphocytic leukemia⁶⁷.

Examples of genetic links between T1DM and cancer are **DQB1*0201, DQB1*0302**.

2. CTLA-4 (cytotoxic T lymphocyte antigen-4)

Polymorphisms of CTLA-4 have been associated with T1DM and with other autoimmune diseases. These polymorphisms lead to decreased intracellular expression of the protein; therefore, excessive stimulation and proliferation of T lymphocytes is not inhibited resulting in uncontrolled progression of immune response and autoimmune imbalance^{68, 69}.

CTLA-4 signaling has been shown to dampen immune responses against infections and tumor cells^{70, 71}. If the CTLA-4 signaling is suppressed, immune response is activated. Anti-CTLA-4 therapies are used against highly immunogenic cancers, such as melanoma⁷². Anti-CTLA-4 therapies can increase the risk of autoimmunity (iatrogenic autoimmunity). Nivolumab and ipilimumab treatment may increase risk of developing autoimmune joint and tissue disease⁷³.

CTLA-4 signaling suppression, whether is caused by genetic polymorphism or by anti-CTLA-4 cancer therapy, is associated with the higher risk for the development of T1DM and other autoimmune diseases.

3. Protein tyrosine phosphatase non-receptor type 22 (PTPN22)

A missense mutation in the PTPN22 gene (C1858T polymorphism; Arg620Trp) was found to be associated with T1DM because it decreases the binding affinity of lymphoid tyrosyl phosphatase (LYP) to inactivating kinase (CSK), leading to uncontrolled T-cell activation and autoimmune reaction^{74, 75}.

Genetic manipulation of PTPN22 expression might enhance the efficacy of anti-tumor T-cell responses⁷⁶.

Systemic inhibition of PTPN22 can enhance the anticancer immunity⁷⁷, but it could also increase the risk for autoimmune diseases, including T1DM.

4. AIRE

Patients with mutations in the AIRE gene (AIRE protein is an autoimmune regulator, a transcription factor which controls the expression of many specific autopeptides), located on the long arm of the chromosome 21 (21q22.3), exhibit autoimmune polyendocrine syndrome 1 (APS 1), also known as APECED syndrome. APE stands for polyendocrine autoimmunity (Addison's disease, hypoparathyroidism, **T1DM**), C stands for candidiasis, ED stands for ectodermal dystrophy^{78, 79}.

Kalra and coworkers showed in their study that AIRE finds differential expression in androgen-dependent and androgen-independent prostate cancer cells. AIRE expression is more in androgen-independent cells due to its regulation by transcription factor Elk-1. These enhanced levels of AIRE modulate the prostate tumor microenvironment by transcriptionally activating a malignancy gene IL-6 in androgen-independent cells. AIRE prevents the cancer cells from anticancer drug-induced death and enhances their invasiveness. AIRE by modulating the cytokine milieu skews the

tumor-associated macrophage polarization towards M2 phenotype with increased CD206 and CD163 expression. Subcutaneous mouse model of prostate cancer revealed AIRE^{+/+} mice forming a palpable tumor and presents lymphadenopathy however, only a small benign tumor is observed in AIRE^{-/-} mice and lymph nodes appear normal in size. In conclusion, these findings suggest AIRE as a probable factor in promoting prostate cancer progression⁸⁰.

Results of another study conducted by Nguyen and coworkers indicate that AIRE is induced in oral squamous cell carcinoma and supports cancer-related gene expression in cooperation with ETS1 (proto-oncogene)⁸¹.

Data from a study conducted by Bianchi and coworkers highlight that AIRE expression in breast cancer is associated with a better prognosis. Imbalance of cellular homeostasis, caused by AIRE transcriptional function, is a new unusual mechanism to trigger apoptosis in breast cancer cells⁸².

5. FoxP3

The gene of the transcription factor FoxP3 encodes for a protein scurfin. In humans, congenital dysfunction of FoxP3 leads to an autoimmune polyendocrine disorder associated with chromosome X (IPEX

syndrome) and is manifested with a milder phenotype comprising of **T1DM**, allergies, enteropathies and eczema⁸³.

FoxP3 transcription factor can be observed as the main component of the immune system expressed in regulatory T (Treg) cells that regulate hemostasis and self-tolerance. The altered expression of FoxP3 was found in autoimmune diseases, benign tumors and carcinomas. Latest reports indicate that the FoxP3 gene mutation can contribute to carcinogenesis, which can be associated with immune response abnormalities⁸⁴. FoxP3 can act as a co-activator to facilitate the Wnt-b-catenin signaling pathway, inducing epithelial–mesenchymal transition, tumor growth and metastasis in non-small cell lung carcinoma⁸⁵. FoxP3 expression is associated with degree of gastric cancer differentiation. Upregulated and ectopic tumoral FoxP3 can promote gastric cancer proliferation, migration, and invasion, partly through the TGF- β pathway⁸⁶.

6. STAT3

Mutations in the STAT3 transcription factor (that is involved in Th1 differentiation) have been identified as monogenic causes of autoimmune diseases. *De novo* activating mutations of STAT3 are associated with an early onset spectrum

of autoimmune diseases, such as **T1DM** and autoimmune thyroid dysfunction⁸⁷.

Aberrant/unrestrained STAT3 activity is detected in a wide variety of tumors, driving multiple pro-oncogenic functions. STAT3 is widely considered as an oncogene, but STAT3 can elicit different and sometimes contrasting effects under different conditions. STAT3 activities have been shown to be either pro-oncogenic or tumor-suppressive according to the tumor etiology/mutational landscape⁸⁸.

STAT3 is persistently activated in melanoma, multiple myeloma, breast, prostate, ovarian, and colon cancers, thus contributing to malignant transformation and progression. STAT3 is an attractive therapeutic target for cancers⁸⁹.

7. HIP14

Knockdown of HIP14 genes (Huntingtin-Interacting Protein 14 gene, located on chromosome 12, encodes for a palmitoyl transferase) in mice revealed increased apoptosis for pancreatic β cells^{90, 91}.

Ducker and coworkers showed in the study that HIP14 is over-expressed in a number of human cancers, including colon, stomach, prostate, lung, and breast. The increase in expression may correlate with increased severity of the disease. HIP14 may be a good pharmacodynamic marker for these diseases, as well as a viable target

for their treatment⁹². High mRNA expression of HIP14 is an unfavorable prognostic marker in renal cancer⁹³.

8. ERBB3

The Erb-B2 receptor tyrosine kinase 3 gene (located on chromosome 12) seems to play an important role in cytokine-induced apoptosis of β cells⁹⁴.

HER3, a member of the EGFR family of receptor tyrosine kinases coded by the ERBB3 gene, plays an important role in cancer, despite its lack of intrinsic kinase activity. Oncogenic ERBB3 somatic mutations are potential tumor drivers⁹⁵.

9. Other genetic factors: insulin-VNTR polymorphism (10% of the genetic predisposition for T1DM, big class allele is protective^{96, 97}) and **IFIH1** (the gene encodes the MDA5 protein, rare variants of IFIH1 through a lost or reduced expression of the protein are protective against T1DM, common IFIH1 single nuclear polymorphisms are associated with the disease^{98, 99}).

OVERLAPPING ENVIRONMENTAL FACTORS IN DIABETES AND CANCER

1. VIRUSES

Children exposed during fetal life to rubella have an increased incidence of

T1DM¹⁰⁰. Enteroviruses can play an important role in the early phase of the development of T1DM through the activation of innate immunity¹⁰¹.

In T1DM, the best studied paradigm of molecular mimicry is the P2-C protein of the Coxsackie B4 virus. Clones from T-cell lines, that recognize both GAD65 (enzyme found in β cells of endocrine pancreas) and P2-C peptides (virus protein), react with both, what results with the destruction of β -cells of the pancreas^{102, 103}.

Viruses also play an important role in the pathogenesis of cancer. For example, human papilloma viruses induce inflammation and are responsible for 90-100% of all cervical cancers¹⁰⁴. Epstein-Barr virus infection can contribute to the origin and maintenance of Burkitt lymphoma¹⁰⁵.

2. DIET

In several studies, associations of early introduction in the infant's diet of cow's milk with an increased risk for the disease have been reported supporting that infant's exposure to insulin contained in the milk is triggering the autoimmune response¹⁰⁶. Early integration of cereals into the diet¹⁰⁷, nitrate exposure from water intake¹⁰⁸, inadequate intake of omega-3 fatty acids¹⁰⁹ and vitamin D deficiency^{110, 111}, have also been implicated.

Pathogens in cow's meat and milk may cause cancer in humans, according to findings from the German Cancer Research Centre (DKFZ). Pathogens dubbed "Bovine Milk and Meat Factors" found in healthy cows may cause a chronic inflammatory reaction in tissues, such as breast and colon, that can promote cancer. These cancers may take decades to manifest after the person consumes the milk or meat from a cow¹¹².

3. GUT MICROBIOTA

Patients with T1DM exhibit differences in their gut microbiota compared to healthy controls, specifically a reduced *Firmicutes* vs. *Bacteroidetes* ratio^{113, 114}.

Gastrointestinal dysbiosis has been linked with both local and distant tumors¹¹⁵.

The product of the cytotoxin associated gene A (CagA) from *Helicobacter pylori*, induces the proteasome-mediated degradation of p53 in gastric epithelial cells, by interfering with the host's AKT pathway, thus promoting the rise of gastric cancer¹¹⁶. *Enterococcus faecalis* produces extracellular superoxide and derivative oxygen species capable to diffuse into host's cells. In turn, the increase in the oxidative milieu enhances the possibility of host's cellular DNA mutations¹¹⁷.

Fusobacterium nucleatum inhibits for its own advantage host's Natural Killer (NK)

cells, in order to recruit at the site of the infection myeloid suppressor cells, therefore indirectly helping cancer genesis¹¹⁸. *Bacteroides fragilis* is able to activate the host's spermine oxidase, which, in turn, generates hydrogen peroxide and reactive oxygen species (ROS)-induced accumulation of DNA damage¹¹⁹.

When gut dysbiosis is coupled with an increase in the β -glucuronidase-secreting bacteria, such as *Clostridium leptum* and *Clostridium coccoides*, the enzyme deconjugates liver-catabolized and plant-derived estrogens, enabling them to bind and activate the estrogen receptors expressed by target cells. Estrogen receptors activation promotes cell proliferation in tissues responding to estrogens, as breast and endometrium^{120, 121}.

LGG (*Lactobacillus rhamnosus* GG) is a very good example of a probiotic well studied in cancer, often administered as complementary therapeutic to cure dysbiosis. Given the observed functions as anti-inflammatory and anti-cancer agent in both cellular and animal models, this probiotic may be suggested to be further characterized as adjuvant in integrated anti-cancer therapies in the future¹²².

CANCER AND TYPE II DIABETES

Type II diabetes is associated with an increased risk for several cancers, including colon, postmenopausal breast, pancreatic, liver, endometrial, and bladder cancers and non-Hodgkin lymphoma. TIIDM is linked to a modest decrease in the risk for prostate cancer, but does not reduce aggressive forms, and prostate cancer mortality rates are higher among men with diabetes¹²³.

Elevated levels of insulin or C-peptide (biomarker of insulin production) predict increased risk for colorectal, postmenopausal breast, pancreatic, bladder, and endometrial cancers^{124, 125}.

Some evidence suggests that cancer cells may be particularly affected by hyperinsulinemia because of an increased concentration of insulin receptors, often in a form that is particularly mitogenic^{126, 127}.

Human population studies link higher levels of IGF-1 (insulin-like growth factor-1), seen in TIIDM, with an increased risk for colorectal and estrogen receptor-positive breast cancer and possibly prostate and other cancers^{124, 125, 128, 129}.

Hyperinsulinemia decreases liver production of sex hormone-binding globulin, which increases estrogen bioavailability, and together with obesity

increases the risk for postmenopausal breast and endometrial cancers^{130, 131}.

TIIDM and obesity are both characterized by chronic low-grade inflammation, which increases production of free radicals that can disrupt insulin signaling and damage DNA, what can lead to cancer^{126, 132}.

Obesity is associated with high levels of leptin and decreased production of adiponectin. Population studies link elevated leptin to increased incidence of colorectal, postmenopausal breast, and potentially other cancers. Reduced adiponectin may promote cancer development through increased insulin resistance and inflammation or through changes in cell signaling that increase cell proliferation and angiogenesis^{127, 133}.

Hyperglycemia increases production of free radicals and other reactive molecules, which could produce oxidative damage to DNA, leading to mutations in oncogenes and tumor suppressor genes¹²⁶.

CONCLUSION

In cancer, corrupted neoplastic cell successfully evades the immune attack using two main strategies: avoiding the immune recognition and instigating an immunosuppressive tumor microenvironment. Cancer is able to

induce immune tolerance and present itself to immune system as normal tissue. There is a defect in immune tolerance: the tolerance is wrongly induced toward cancer. In autoimmune diseases, immune system attacks normal tissue because it fails to recognize its own constituent parts as self. There is a defect in immune tolerance: the tolerance is lost toward normal tissues.

In both diseases wrong information in the communication between tissue (neoplastic) cells and immune system is crucial: in cancer, neoplastic cells avoid immune attack, whilst in autoimmune diseases, immune system attacks normal cells.

Wrong information is written in human genome as mutation (genetic susceptibility for either cancer or autoimmune diseases) and is translated on the molecular level after a second hit (infection, toxins, radiation, protein-energy malnutrition, deficiencies of trace minerals and vitamins, psychological stress, chronic inflammation, tobacco, obesity, diabetes, alcohol abuse...). Although cancer and autoimmune diseases are based on completely different type of wrong information, both diseases are associated with chronic inflammation.

Autoimmune diseases are associated with an increased risk of developing some solid

tumors and hematologic malignancies. Immune therapy used in some types of cancer is associated with an increased risk of developing iatrogenic autoimmune diseases. Therefore, the art of immunomodulatory therapies is to find a balance between achieving both anticancer and anti-autoimmune effect.

Diabetes mellitus type I and II are associated with an increased risk of developing different types of cancer. Pathogenesis of diabetes mellitus type I and pathogenesis of cancer overlap in genetic, environmental and immunologic factors. Diabetes mellitus type II and obesity can both induce oncogenesis. Protective factors for both diabetes and cancer overlap, such as healthy balanced diet with optimal level of micronutrients, ideal body weight, healthy gut microbiota, antioxidant therapy, avoidance of toxin exposure and prevention of some bacterial and viral infections (*Helicobacter pylori*, HPV, EBV, Enteroviruses, Coxsackie B4 virus, gastrointestinal dysbiosis).

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