Apoptotic Pathways, Cell Cycle Regulation and Cancer Progression: Review

Apopitotik Yolaklar, Hücre Döngüsünün Düzenlenmesi ve Kanser Progresyonu

Georgi TCHERNEV, MD[a]

[a]Department of Dermatology, Venerology and Dermatosurgery MVZ Kirchheim GmbH, Steingaustr. 13, 73230 Kirchheim/Teck, Germany

Geliş Tarihi/*Received:* 06.11.2008
Kabul Tarihi/*Accepted:* 03.06.2009

Yazışma Adresi/*Correspondence:*
Georgi TCHERNEV, MD
Department of Dermatology, Venerology and Dermatosurgery MVZ Kirchheim GmbH, Steingaustr. 13, 73230 Kirchheim/Teck, Germany
georgi_tchernev@yahoo.de

ABSTRACT The mechanisms of tumor cell survival are regulated by overcoming cell cycle checkpoints and immunological responses. These mechanisms are main part of uncontrolled local tumour growth and tumour progression.The exact course and succession of the mechanisms allowing the tumor cells to survive and remain undisturbed, as well as to proliferate and to produce metastases are not exactly clear yet. In the cases of the so called endogen tumour escape, the elimination of the reparative systems, which directly participate in the induction of the cellular block is of primordial importance. The additional suppression of the apoptosis at cellular level and its activation in the cell of the immune system create the conditions of unblocked proliferation of the tumor cells. The interactions between proliferating tumour cells, HLA-I system and NK-receptors are probably at the origin of the so called exogenous form of tumour escape. The final result of these interactions consists of the impossibility of the early elimination of the tumor. The disturbances of cell proliferation, differentiation and apoptosis are based on specific and incompletely characterized signal-transduction pathways within the tumor cells and between them and the immune system. In the near future more detailed investigations and characterizations of the mechanisms involved are required to describe better the tumor behavior and to prepare more reliable prognosis with the purpose to suggest new therapeutic strategies.

Key Words: Cell cycle, Bax, p53, apoptosis, Bcl-2, Rb

ÖZET Tümör hücresinin hayatta kalma mekanizmaları hücre döngüsü kontrol noktalarının aşılması ve immunolojik yanıtlarla düzenlenir. Bu mekanizmalar kontrolsüz lokal tümör büyümesi ve tümör progresyonunun ana bileşenleridir. Tümör hücrelerinin yaşamalarına ve sarsılmadan kalmalarına, aynı zamanda da çoğalmalarına ve metastaz yapmalarına yol açan bu mekanizmalardaki kesin süreç ve silsile tam anlamıyla açık değildir. Endojen tümör kaçışı (endogen tumour escape) olarak adlandırılan durumlarda hücresel bloğun indüksiyonuna direk olarak katılan onarım sistemlerindeki eliminasyon öncelikli olarak önemlidir. Apopitozun hücresel düzeyde ek olarak baskılanması ve immun sistem hücrelerinde ise aktiflenmesi tümör hücrelerinin kontrolsüz çoğalması durumunu yaratır. Çoğalan tümör hücreleri, HLA-I sistemi ve NK-reseptörleri arasındaki etkileşimler tümör kaçışının eksojen formu olarak adlandırılan durumun başlangıcı olabilir. Bu etkileşimlerin en önemli sonucu tümörün erken eliminasyonunun imkansızlığıdır. Hücre çoğalması, ayrımlaşması ve apopitozdaki bozukluk tümör hücreleri içinde ve birbirleri arasında ve immun sistem ile aralarında bulunan spesifik ve tam anlamıyla aydınlatılamamış sinyal ileti yolakları temelindedir. Yakın gelecekte söz konusu mekanizmaların çok detaylı araştırılması ve tanımlanması tümör davranışının daha iyi açıklanması ve yeni tedavi stratejileri ile daha iyi prognoz elde edilmesi için gereklidir.

Anahtar Kelimeler: Hücre döngüsü, Bax, p53, apoptoz, Bcl-2, Rb

Turkiye Klinikleri J Med Sci 2009;29(4):952-8

The tumor escape is the main obstacle, leading to progression of tumor growth and to ineffectiveness of immunotherapy and chemotherapy.[1,2]

The concept of tumor escape can be connected with the so called mechanism exogenous tumor escape-due to the escape of the tumor cells from the immune response of the organism (by means of different mechanisms), on one part, and on the other part-due to some disregulation in the processes of cell proliferation and apoptosis (endogenous tumor escape), which lead to some advantages in the selection of new tumor branches.[3-7] Decreased apoptosis in the tissue (non-immunlogic type of tumor escape, endogenous form) could be accompanied by increased apoptosis of lymphocytes in the peripheral blood or by down or deficient regulation of certain HLA-I molecules (immunologic or exogenous form of tumor escape).[8] According to other authors, even the tumor itself is able to counterattack the tumor-infiltrating lymphocytes and to eliminate them.[9,10] Perhaps the combination of both forms of tumor escape better explains the processes of cancer genesis.[11-13] Although several in vitro researches show the efficiency of congenital and acquired immunity in the elimination of tumor cells, in vivo, these tumors remain untouched in many of the cases, by effector systems of the immune system. The reasons of this phenomenon maybe must be searched in the failure of immunity to overcome the quickly proliferating tumor cells, in the production of certain humoral factors derived from the tumor (the ones which block the T- and/or B-mediated cell immunity), and in the dysfunction of the T-cells, which may have a different genesis.[14,15]

It is also possible, within the immune response, an injury of own cells of the organism to take place by means of the so called antigen mimicry, when tissue antigens, structurally analogous to tumor cells are recognized by T- or B-cell immunity as strangers and consequently, are attacked by them.[16]

The presence of killer immunglobuline receptors (KIR) on the T-lymphocytes themselves and their indirect blocking by tumors, as well as the inherent property of the tumors to escape from the programmed cell death-by autocrinouse secretion of Fas L for instance, is at the root of the exogenous tumor escape.[17-20]

The problem of how to solve the abovementioned peculiarities is complex and includes a detailed study of the signal chains activating and inactivating immunity, as well as some inhibiting factors, which directly or indirectly, contribute to the tumor escape.[21] The simultaneous determination of the causes of the uncontrolled cell proliferation too, and the impossibility to activate the programmed cell death (apoptosis) additionally make the interpretation of pathologic genetic concepts more complicated.[7]

CELL CYCLE REGULATION, APOPTOSIS AND TUMOR ESCAPE

The disregulation or disorders arising within the limits of the cell cycle which have not been removed by means of the cell-proliferation modulators and proapoptotic representatives of the Bcl-2 protein family lead to persistence and selection of new tumor branches which makes the malign transformation more potent (Figure 1, 2).[6,7] This way, conditions of independent and unhindered tumor evolution are created.

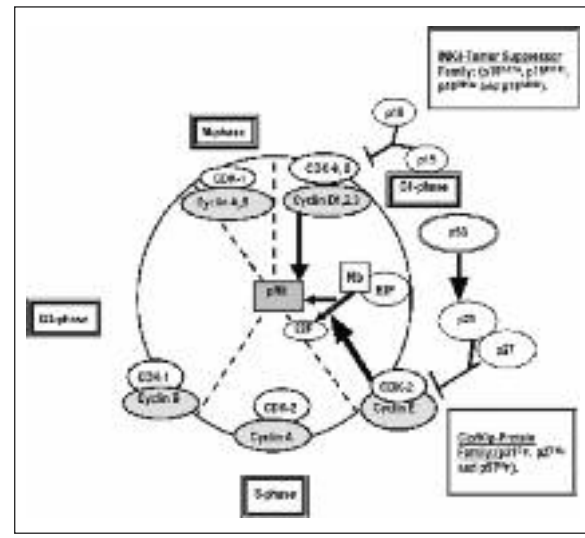

FIGURE 1: p53 and its role in the regulation of the cell-cycle "engine" [modified after 20]. The regulation of the CDK activities in different phases of the cell cycle controls the correct process of DNA synthesis and replication.

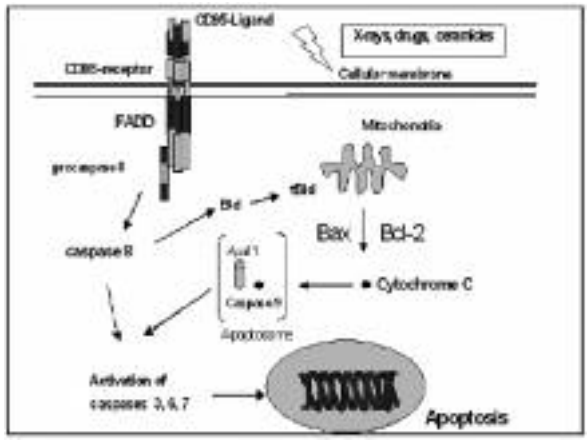

FIGURE 2: Pathways for induction of apoptosis: direct activation of the CD95 receptor by means of CD95 ligands and indirect damaging of the cell membrane induced by drugs, X-rays, ceramides. Of crucial importance is the expression of pro-and antiapoptotic proteins like Bax and Bcl-2 having impact on the permeability of the mitochondrial membrane [modified after 18,19]. The proteins of the Bcl-2 family modulate the behavior of the tumor tissue within the limits of the endogenous tumor escape. The low regulation of the proapoptotic proteins, such as Bax and Bak is, probably important for the persistence and selection of aggressive tumor branches.[16,17] Determining single molecules as prognostic parameters within cancer genesis is incorrect. The simultaneous detection of more marker molecules characterizing the processes of proliferation and apoptosis (in combination with mutation analysis), and the characteristics of the T-cellular effector systems and the HLA-I status (participants in the exogenous tumor escape), will give a more precise description of the real status and probably will become routine in the close future.

The genome instability in tumor tissue is due to the disregulation of the so-called "checkpoints" of the cell cycle (Figure 1).[22] The representatives of Cip, Kip and INK4-tumor suppressing families are the effector molecules within these checkpoints. The main representatives of these families are: $p21^{Cip}$, $p27^{Kip}$, $p57^{Kip}$ $p16^{INK4a}$, $p15^{INK4b}$, $p18^{INK4c}$ and $p19^{INK4d}$ (Figure 1).[6,7]

Complex signal transduction systems-called checkpoints-could regulate growth arrest, DNA-repair and apoptosis and thereby prevent the formation of tumor cells.[6] Rb is an inhibitor of cell proliferation. CDKs are essential components of the cell-cycle engine (Figure 1). Rb has two important tasks: it induces blockage of the cell cycle and keeps the apoptosis at bay. In this process, proliferation is blocked by Rb through repression of cyclin E, cyclin A and Cdc-2 genes. The promoters of these proteins possess specific E2F binding sites. By repressing the expression of these genes, Rb can block the cell proliferation. Rb is an important downstream effector in the p53/p21Cip1 pathway, and Rb can arrest damaged cells in the G1-, S- or G2-phases of the cell cycle (Figure 1).[6,7,23] The activation of p53/p21 leads to inhibition of the cell cycle, and the tumor suppressor protein Rb rests in its hypophosphorylated or active form that binds E2F (pRb= hyperphosphorylated, inactive form; Rb= hypophosphorylated, active form). The tumor suppressor protein in retinoblastoma (Rb) is one of the major proteins that can cause blockage of the cell cycle. Rb is capable of inhibiting the transcription factor E2F and c-Abl tyrosine kinase. Thus, Rb attacks through indirect inhibition of E2F in the cell cycle (Figure 1).[6,23]

The presence of defects affecting the regulators of these "transition points" makes the removal of certain anomalies, which are still affecting the cells that are "subject to malignant transformation", impossible. The tumor cells, as their content is heterogeneous begin to persist in the genome.[6] This probably underlies the generation of immunoresistant tumor formations, which initially escape from the internal cell-controlling mechanisms.[6,23] It is quite correct to denominate this phenomenon as an endogenous tumor escape. The exact mechanisms according to which the control on cell proliferation and programmed cell death are avoided are not completely clarified.[7] The endogenous form of the already mentioned phenomenon precedes the exogenous one.

The exogenous form of tumor escape needs the participation of the interaction between different forms of inducting and executive systems, including the HLA-system and the T-cell immunity.[24-26]

The reasons making the activation of the programmed cell death impossible are various. Death receptors playing a key role in the activation of the exogenous or external apoptous tract may result affected (activated/blocked) (Figure 2).[4,5,27] The location of these receptors may be either in the tumor cells themselves, or in the peripheral lymphocytes as well (Figure 2).[28-30] Precisely this link shows the unbreakable connection between the exogenous

and endogenous forms of the tumor escape, as well as between the processes of uncontrolled cell proliferation, apoptosis and malignant transformation.

Each injury of the gene of the multidomained proapoptotic protein Bax can lead to disorders in the internal mitochondria tract and contribute to the tumor progression.[5,6,23] The misbalance in the expression of the pro- and antiapoptotic representatives of Bcl-2 protein family in the mitochondria apoptosome is capable to give advantage to tumor cells and by indirect means to help the tumor escape.[5,6,23]

It is considered that certain genetic alterations affecting the expression of the pro- and antiapoptotic genes and molecules (*Bax, Bak* and Bcl-2), as well as the modulators of the cell cycle (p21, p27, p53 and Rb), underlie the tumor progression.[6,7] The qualitative and quantitative appraisal of the already mentioned proteins in the primary tumor tissue would be able to provide an important information about the risk of a possible tumor progression and the surviving capacity of the patients.[7]

Although the presence of micro-satellite instability plays an important role for the development of some tumors, the finding of mutations of the proapoptotic proteins and the regulators of the cell cycle are not always the leaders of their evolution.[22] Frequently, the modifications arise at later stages, during the so-called advanced stage.[22] The reduced expression of certain pro-apoptotic proteins, such as Bax an Bak probably leads to the selection of different cell branches, and some of them are capable to produce proteins with inhibiting effect on the immune system.[6,7] This way the genetic instability, the impossibility to induce the programmed cell death and the tumor escape are mutually empowered.[6,7]

According to other authors, the reduced apoptosis in the tumor is accompanied by increased apoptosis of the tumor-like infiltrating mononuclear cells, and this indirectly helps the uncontrolled proliferation (Figure 2).[3] The immune system is practically inactivated.[3]

An interesting example for exogenous form of tumor escape and its link with the apoptotic processes may be the autocrinic secretion of Fas-L, which protects the tumor cells from the Fas-mediated apoptosis (mediated by the cytotoxic lymphocytes).[9,15,27,31] In the cases of melanomas of the vascular coat of the eye, the tumor cells exhibit Fas-receptor, but they are insensitive not only with respect to the T-cell mediated apoptosis, but also to the apoptosis mediated by the Fas-specific antibodies with agony provoking effect. The melanomas of the uvea become sensitive to the Fas-mediated apoptosis only after a treatment by metaloproteatic inhibitors. This way, the autocrinic secretion of the Fas-L protects the tumor cells from the cytotoxic lymphocytes and with a great deal of justification may be analyzed as a form of tumor escape of exogenous nature that does not affect directly the tumor cells.

KILLER RECEPTORS IMMUNOGLOBULIN- AND LECTIN-LIKE RECEPTORS AND THEIR RELATIONSHIP TO TUMOR ESCAPE

KIR-receptors are located in the plasmatic membrane of the natural killer (NK) cells and they participate in the detection and elimination of tumor cells. The KIR-genes belong to the gene superfamily located in chromosome 19 (19q13.4).[2,8,12] They are responsible for the expression of KIR-receptors on NK cells. Fourteen different KIR-receptors have been identified in the human body, of which eight have inhibiting and six activating, or ITAM effects. The inhibiting receptors possess a long cytoplasmic part containing ITIM fragments.[12] The KIR-family receptors possess both activating and blocking effects.[12,13]

Another type of receptor molecules which have an impact on the function of the NK cells and are located on their surface, are the C-type-Lectin-Like-Receptors, belonging to natural killer gene complex (NKC).[2,8] By analogy with the KIR receptors, they also have both activating and inhibiting function in the transmission of the respective signals. Five types of Lectin-Like-Receptors have been discovered in the human body, expressed as

hetero- or homodimers. These receptors are also suggested to play a key role in tumor escape.[2,13]

The presence of immune-receptor thyrously based inhibiting sector (ITIMs) in the cytoplasmic area is characteristic for the structure of the KIR- and lectin-like-receptors transmitting an inhibiting signal.[8]

The activating receptors of both groups structurally differ from the inhibiting receptors. The latter contain amino-acidic sector located in the transmembranous area of the cell, additionally allowing the association of the adaptor molecules, such DAP-10 and DAP-12. Adaptor molecules possess immuno-receptorial-thyrously-based- activating-areas (ITAMs), which are responsible for the transmission of activating signal after the association with the respective ligand. Most of the inhibiting receptors of the NKC have affinity to HLA-I molecules, while the inhibiting natural killer receptor identify fragments analogous to the HLA-I molecules, such as HLA-G for instance.[2,8,13]

Tumor escape is considered to be generated by direct or indirect changes affecting the KIR- and/or lectin-like-receptors, and by their interaction with the representatives of the HLA-system (Table 1).[13,25] The association of HLA-I with the inhibiting KIR-receptors of the NK cells generates an inhibiting signal to the cells of the immune system, and this way, this association protects the normal cells from immune reaction.[7]

Some malignant cells have the ability to decrease the expression of the HLA-I system and thus indirectly to avoid the transmission of an activating signal to the NK cells and this, in consequence, should lead to their further elimination.

Another possibility of tumor escape is the association of the NK cells with proteins analogous to the HLA molecule (HLA-G, for instance). The HLA-G isoform is structurally a typical HLA-I molecule, containing alpha -1, -2 and -3 extracellular domains, which are incovalently associated with beta-2-microglobulin.[32,33] The HLA-G1-isoform has been discovered in the form of membrane- associated protein, located on the cellular surface. The HLA-G protein is a key mediator in the development of immune tolerance not only in the case of tumors, but also in a number of immunologic diseases.[32-34]

Not only for the inhibition, but also for the activation of the KIR-receptors, the participation of certain HLA molecules in the form of ligaments is necessary. The modifications affecting the HLA molecules within the cancer genesis are considered to be among the basic generators of the tumor escape. The HLA-G molecule plays its role in different immune processes and autoimmune diseases and in some cases it blocks the T-lymphocytes during pregnancy, thus protecting the semi-allogeneic fetus from immunologic attack by means of the maternal lymphocytes.[26]

The high regulation of the inhibiting HLA-G molecule in some tumors (glioma and kidney carcinoma) confirms its essential importance in the processes of malignant transformation.[19]

HLA-G may be detected not only in tumor cells, but also in macrophagocytes and the T-cells of other carcinomas.[19,22,32,34]

The expression of the HLA-G molecule in patients with melanoma metastasis underlies the tumor progression because of the impossibility of direct activation of the NK-cells.

CONCLUSIONS

1. The establishment of a rigorously defined dogma of behavior for tumor cells in every kind of tumor, as well as in each individual is problematic.

2. The determination of single molecules as prognostic parameters within cancer genesis is incorrect and wrong. The simultaneous detection of more marker molecules characterizing the processes of proliferation and apoptosis (in combination with mutation analysis) , and the characteristics of the T-cellular effector systems and the HLA-I status, give a more precise description of the real status and, probably, will become routine in the close future.

3. The differences in the receptor repertoire of the NK cells in all individuals, as well as the proportion between inhibiting and activating receptors of

TABLE 1: The interaction between KIR-receptors and KIR-ligands.

KIR-receptors	HLA-ligands for KIR- receptors
KIR 2DL1	HLA Cw4 HLA-Cw6 HLA-C
KIR 2DL2	HLC Cw1 HLA-Cw3 HLA-Cw7
KIR 2DL3	HLA Cw1 HLA-Cw3 HLA-Cw7
KIR 2DL4	Not known yet
KIR 2DC1	HLA Cw4
KIR 2DC2	Not known yet
KIR 2DC3	Not known yet
KIR 2DC4	HLA C
KIR 2DC5	Not known yet
KIR 3DL1	HLA Bw4
KIR 3DL2	HLA A
KIR 3DC1	HLA B

KIR: Killer immunglobuline receptors.

each T-cell is of decisive importance for the activation of the T-cellular immunity and the removal of the tumor formations at optimal conditions.[30]

4. Taking into consideration the fact that certain branches of the antigen-specific cytotoxic T-lymphocytes (such as Mage A10 CD8 (+)) persists during years and years and that they probably are responsible for the lack of recurrences of certain tumours, the description of the exact profile of these cells as well as the discovery of other similar cells) could be probably of primordial importance. The passive transfer, or the direct stimulation of such cellular sub-branches (in the respective tumour profile, according to the immune compatibility between donor and acceptor) would be an adequate and possible therapeutic option.

5. Any unilateral conclusions based on results which count on the processes of apoptosis and proliferation are not enought due to the fact that tumour cells could be neutralized by immunologic mechanisms at "higher" immunologic level.[15,35] Thus, the regulators of the endogenous tumour escape acquire primordial importance, and the elimination of the tumour takes place due to cellular interactions at "another level", which are not taken into consideration in the respective investigation. This probably, is the reason of the significant differences in the choice of suitable prognostic parameters within the limits of cancer genesis.

The processes of regulation of the apoptosis, the cell proliferation and the inactivation of the immune system are closely linked with the different forms of the tumour escape.

Acknowledgement

No sources of funding were used to assist in the preparation of this review. The author has no conflicts of interest that are directly relevant to the content of this review.

REFERENCES

1. Ahmad M, Rees RC, Ali SA. Escape from immunotherapy: possible mechanisms that influence tumour regression/progression. Cancer Immunol Immunother 2004;53(10): 844-54.
2. Paweleg G. Tumour escape: antitumour effectors too much of a good thing? Cancer Immunol Immunother 2004; 53(3):262-74.
3. Chen GG, Lee JF, Chan UP, Xu H, Ip PC, Lau WY. Increased apoptosis in infiltrating mononuclear cells of colorectal cancer: a mechanism for tumour escape. Arch Pathol Lab Med 2002;126(6):686-91.
4. Daniel PT. Dissecting the pathways to death. Leukemia 2000;14(12):2035-44.
5. Daniel P, Wieder T, Sturm I, Schulze-Osthoff K. The kiss of death: promises and failures of death receptors and ligands in cancer therapy. Leukemia 2001;15(7): 1022-32.
6. Funk JO, Kind P. [Cell cycle control, genetic instability and cancer]. Hautarzt 1997; 48(3):157-65.
7. Tchernev G, Orfanos CE. Downregulation of cell cycle modulators p21, p27,p53, Rb and proapoptotic Bcl-2 related proteins Bax and Bak in cutaneous melanoma is associated with worse patient prognosis. J Cutan Pathol 2007; 34(3): 247-56.
8. Malmberg KJ, Ljunggren HG. Escape from immune- and nonimmune-mediated tumor surveillance. Semin Cancer Biol 2006;16(1): 16-31.
9. Igney FH, Krammer PH. Tumour counterattack: fact or fiction? Cancer Immunol Immunother 2005; 54(11): 1127-36.
10. Khong HT, Restifo NP. Natural selection of tumour variants in the generation of "Tumour escape" phenotypes. Nat Immunol 2002; 3(11):999-1005.
11. Gajewski TF.Identifying and overcoming immune resistance mechanisms in the melanoma tumor microenvironment. Clin Cancer Res 2006;12:2326-30.
12. Le Gal FA, Widmer VM, Dutoit V, Rubio-GodoY V, Schrenzel J, Walker PR, et al. Tissue Homing and Perssistence of Defined Antigen-Specific CD(+) Tumor-Reactive T-Cell Clones in Long Term Melanoma Survivors. J Invest Dermatol 2007;127(3): 622-9.
13. Poggi A, Zocchi MR. Mechanisms of tumour escape: role of tumour microenvironment in inducing apoptosis of cytolytic effector cells. Arch Immunol Ther Exp (Warsz) 2006; 54(5): 323-33.

14. Ghebeh H, Mohammed S, Al-Omair A, Qattan A, Lehe C, Al-Qudaihi G, et al. The B7-H1(PD-L1) lymphocyte–inhibitory molecule is expressed in breast cancer patients with infiltrating ductal carcinoma: correlation with important high-risk prognostic factors. Neoplasia 2006;8(3):190-8.
15. Hallermalm K, De Geer A, Kiessling R, Levitsky V, Levitskaya Y. Autocrine secretion of FAS ligand shields tumor cells from Fas-mediated killing by cytotoxic lymphocytes. Cancer Res 2004;64(18):6775-82.
16. Tchernev G, Orfanos CE. Antigen mimicry, epitope spreading and the pathogenesis of pemphigus. Tissue Antigens 2006; 68(4):280-6.
17. Abrams SI. Positive and negative consequences of Fas/Fas ligand interactions in the antitumour response. Front Biosci 2005; 10:809-21.
18. Bahri R, Hirsch F, Josse A, Rouas-Freiss N, Bidere N, Vasquez A, et al. Soluble HLA-G Inhibits Cell Cycle Progression in Human Alloreactive T Lymphocytes. J Immunol 2006;176(3):1331-9.
19. Bukur J, Rebmann V, Grosse-Wilde H, Luboldt H, Ruebben H, Drexler I, et al. Functional Role of Human Leucocyte Antigen G Up-Regulation in Renal Cell Carcinoma. Cancer Res 2003;63(14):4107-11.
20. Barrier BF, Kendall BS, Ryan CE, Sharpe-Timms KL. HLA-G is expressed by the glandular epithelium of peritoneal endometriosis but not in eutopic endometrium. Hum Reprod Update 2006; 21(4):864-9.
21. Carosella ED, Rouas-Freiss N, Paul P, Dausset J. HLA-G: a tolerance molecule from the major histocompatibility complex. Immunol Today 1999; 20:60.
22. Cao S, Chang KH, Luthra R, Liu J. Frameshift Mutations in the Bax Gene Are not involved in Development of Ovarian Endometroid Carcinoma. Mod Pathol 2003;16(10):1048-52.
23. Fecker LF, Geilen CC, Tchernev G, Trefzer U, Assaf C, Kurbanov BM, et al. Loss of proapoptotic Bcl-2 Related Multidomain Proteins in Primary Melanomas Is Associated with Poor Prognosis. J Invest Dermatol 2006;126(6): 1366-71.
24. Hviid TVF. HLA-G in human reproduction: aspects of genetics, function and pregnancy complications. Hum Reprod Update 2006;12(3):209-32.
25. Rouas-Freiss N, Marchal R, Kirszenbaum M, Dausset J, Carosell ED. The a1 domain of HLA-G1 and HLA-G2 inhibits cytotoxicity induced by natural killer cells: Is HLA-G the public ligand for natural killer cell inhibitory receptors? Proc Natl Acad Sci USA 1997;94(10):5249-54.
26. Wiendl H, Feger U, Mittelbronn M, Jack C, Schreiner B, Stadelmann C, et al. Expression of the immune-tolerogenic major histocompatibility molecule HLA-G in multiple sclerosis: implications for CNS immunity. Brain 2005; 128(Pt 11): 2689-704.
27. Ibrahim R, Frederickson H, Parr A, Ward Y, Moncur J, Khleif SN. Expression of FasL in squamous cell carcinomas of the cervix and cervical intraepithelial neoplasia and its role in tumour escape mechanism. Cancer 2006; 106(5):1065-77.
28. Lanier L, Phillips J. Inhibitory MHC class I receptors on NK cells and T cells. Immunol Today 1996;17(2):86-91.
29. Zhang H, Rosdahi J. Expression of oncogenes, tumour suppressor, mismatch repair and apoptosis–related genes in primary and metastatic melanoma cells. Int J Oncol 2001;19(6):1149-53.
30. Valiante NM, Uhrberg M, Schilling HG, Lienert-Weidenbach K, Arnett KL, D'Andrea A. Functionally and structurally distinct NK cell receptor repertoires in the peripheral blood of two human donors. Immunity 1997;7(6):739-51.
31. Chouaib S, Thiery J, Gati A, Guerra N, El Behi M, Dorothee G, et al. Tumor escape from killing: role of killer inhibitory receptors and acquisition of tumour resistance to cell death. Tissue Antigens 2002;60(4): 273-81.
32. Tong Q, Liu K, Wang G. Fas L expression in colorectal carzinoma and its significance in immune escape of cancer. J Huazhong Univ Sci technolog Med Sci 2006; 26(1):79-81.
33. Urosevic M, Trojan A, Dummer R. HLA-G and its KIR ligands in cancer- another enigma yet to be solved ? J Pathol 2000;196(3):252-3.
34. Wiendl H, Mitsdoerffer M, Hofmeister V, Wischhusen J, Bornemann A, Meyermann R, et al. A Functional Role of HLA-G Expression in Human Gliomas: An Alternative Strategy of Immune Escape. J Immunol 2002; 168(9): 4772-80.
35. Trapani JA, Smyth MJ. Report on apoptosis and immunity, 31 May-3 June 2005, Palm Cove, Queensland, Australia. Immunol Cell Biol 2006;84(1):1-5.