The Fas/FasL pathway in cancer pathogenesis

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Apoptosis pathways are being heavily investigated in basic cancer researches, it is now known that tumour cells develop some defence mechanisms to get rid of apoptotic signals or to induce apoptosis of tumour specific lymphocytes and so genes that control apoptosis have a profound effect on malignant phenotype. Fas/FasL system is known as one of such systems that tumour cells use. This pathway is also very important in therapeutic aspects; there are chemicals and drugs that are known to cure malignancy tendencies effecting that pathway. And there are also researches about that apoptotic pathway that concludes the contribution of Fas/FasL pathway on proliferative and/or metastatic capacity of cancers.

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Apoptosis is a form of programmed cell death that is essential for embryonic development, tissue repair and remodelling, and also in pathophysiology of some disorders. It is assumed that there are two convergent apoptotic pathways: the intrinsic one in response to release of mitochondrial products such as cytochrome and the extrinsic one occurring in response to activation of specific cell membrane receptors termed as "death receptors". Important physiological mediators of apoptosis are members of the tumor necrosis factor (TNF) / nerve growth factor (NGF) receptor superfamily including TNF R1, TNF RII, low affinity NGF receptor, B cell antigen CD40 and one of the most important members, the Fas receptors. So Fas (Apol = CD95) is a type I membrane protein of 48 kDa consisting of 335 aminoacids which belongs to one of the subfamilies of death receptors which is part of the TNF-receptor superfamily. And a negative regulatory role has been suggested for the C-terminus of Fas because the deletion of the last 15 aminoacids of Fas increases the sensitivity towards Fas-mediated apoptosis.

Under physiological conditions, Fas-mediated apoptosis is induced by ligand of this receptor, FasL, a TNF-related type II transmembrane molecule. This molecule triggers the apoptosis pathway in a Ca+2-independent fashion by Fas-FasL interaction.

Fas/FasL system is also known as one of the systems that tumour cells use. Apoptosis pathways are being heavily investigated in basic cancer researches, it is now known that tumour cells develop some defence mechanisms to get rid of apoptotic signals or to induce apoptosis of tumour specific lymphocytes and so genes that control apoptosis have a profound effect on malignant phenotype. Fas receptor is known to be widely expressed in various tissues but FasL is especially expressed on cells of immune system such as activated T-cells and Natural Killer cells and also on the cells of immune privileged areas. Reduced expression of Fas and/or increased expression of Fasl is known to exist in some cancer types (including lung cancer), so Fas/FasL system may play very important roles in can-
cancer course. This means that the tumour cells with ability of expressing Fasl take advantage not to be damaged by infiltrating lymphocytes, so this builds an immune privilege for the tumour. Lack of cell surface Fas expression is one of the main routes of apoptotic resistance as mechanism of tumorigenesis and tumor progression. It is thought that there were two ways of Fas/FasL system in cancers: 1) Since FasL on T-lymphocytes can promote apoptosis in Fas-expressing cancer cells, this system can play important roles in cell-mediated cytotoxic reactions against malignant cells; 2) Malignant cells can escape from immune system by downregulation of FasL and by killing the lymphocytes using the expression of Fasl.

Some in vivo models proved that the tumour cells with ability of expressing Fasl take advantage not to be damaged by infiltrating lymphocytes; so this builds an immune privilege for the tumour.

Fasl is a ~37 kDa protein and it can be cleaved into 26-kDa soluble form by metalloproteinases. Both of its forms have the ability to trimerize and then bind to their receptor, Fasl4. But it is known that the membranal form is more efficient than soluble form.

There is a soluble form of Fas that is produced from the membranes of malignant cells lacking 21 aminoacid residues produced by alternative splicing. Soluble Fas (sFas) is thought to be inhibitor for Fasl by competion with membrane-bound form, and so prevents apoptosis. sFas was found in the circulatory system of hepatocellular carcinoma, colon cancers, pancreatic can be increased in some hematopoeitic malignensies, but it is known that the membranal form is more efficient than soluble form.

Fasl pathway is known to be very important also in therapeutic aspects; there are chemicals and drugs that are known to cure malignancy tendencies using that pathway. And there are also researches about that apoptotic pathway that concludes the contribution of Fas/FasL pathway on proliferative and/or metastatic capacity of cancers. Shimizu et al. mentioned that serum soluble Fas and Fasl played important roles in proliferation and metastasis of small cell lung carcinoma patients; and there are lots of other investigations that supports that hypothesis for various kinds of cancers.

So it is thought that functional mutations in Fas and Fasl genes that impair apoptotic signal transduction can be associated with susceptibility to cancers and/or prognosis of malignancy, there are several studies on different kinds of cancers evaluating the relationship between risk of developing malignancy and genetic polymorphisms. Two of such transition mutations in Fas gene are G‡A at position -1377 and A‡G at position -670, 8,10. The former is located within an Sp1 transcriptional factor binding site in the promoter region of the Fas that abolishes the consensus sequence for binding of transcription factor SP-1, 8,10. And also a T‡C transition has been determined at position -844 in the promoter region of Fasl gene. It was thought that higher basal expression of Fasl is significantly associated with the Fasl -844C allele compared with the -844T allele.

In conclusion, polymorphism studies of Fas/Fasl pathway can illustrate the tumorigenesis pattern in various kinds of cancers. And by determining the Fas and/or Fasl gene status of individuals, perhaps it will be possible to predict the fate of tumor progression before designing the treatment procedures. So it will be better to evaluate by further studies.

References


