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LETTER TO THE EDITOR

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IMPLICATION OF PROTOCADHERIN-PC IN THE PROGRESSION OF THE ADVANCED PROSTATE CANCER

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Dear Editor,

Prostate cancer is one of the most frequent diagnosed malignancies in men of Western Countries. This tumor develops and progresses under the influence of androgenic steroids. The basic molecular mechanisms underlining the development and the progression of the disease remains poorly described [1, 2]. However, many research attempts exist concerning the identification of potential genetic loci associated with familial forms of prostate cancer [1, 3]. Nowadays, there is no radical curative therapeutic approach for the advanced forms of this pathological entity of the prostate gland. The identification of the molecular mechanisms implied in the neoplastic progression of the disease is thus of primary importance for the development of new therapeutical options [4]. Relatively recently, de la Taille et al. [5] and Yang et al. [6] identified a new way of indication implied in the acquisition of resistance concerning the hormonal treatment of prostate cancer with the discovery and the characterization of a new protocadherin, the protocadherin-PC. The expression of this molecular structure is induced during the androgenic suppression [5, 6]. Protocadherin-PC is expressed in a preferential way by the neoplastic cells of the hormonoresistant prostate cancer. The increase in the form of the protocadherin-PC allows the tumor cells of the prostate cancer sufferers to resist the apoptosis, to survive and proliferate in the total absence of androgens. Indeed, the protocadherin-PC expression in a stable way by LNCaP cells, allow them to proliferate and form soft agar colonies in a medium impoverished of hormone as well as to form tumors in the castrated mice nudes [5]. These data imply the role of the protocadherin-PC in the transition from the hormone-sensitivity of the LNCaP cells towards hormone-resistance. The study of its functions showed that the protocadherin-PC in addition, inhibits the transcription activity of the receiver of the androgens by inducing its degradation [6]. An abnormal distribution of the β-catenin at the cytoplasmic and nuclear level in the cells with selective expression the protocadherin-PC (LNCaP-TR lines and — SSR), has been documented [5]. By the transitory technique of transfection, it has been found that protocadherin-PC is directly implied in the modification of the intracellular distribution of the β-catenin [6]. It was clearly shown that accumulation of the β-catenin in the cytoplasm of neoplastic cells supports its translocation in the core and its connection with the transcription factors of the Tcf/Lef family. These molecular complexes are able to control the cellular proliferation of the tumor cells and inhibit apoptosis by activating genes coding for proteins like c-myc and of cycline D1 [7, 8]. It has been also observed that the delocalization of the β-catenin by the protocadherin-PC supports the transcription activity of the Tcf/Lef transcription factor in neoplastic prostate cells. It is very interesting to note that the activation of Tcf/Lef pathway by the protocadherin-PC is observed in other malignant cell lines. By using a chip of cDNA it was demonstrated that the Wnt pathway is also activated by protocadherin-PC by inducing some members like WNT3, 7B, 1 DA 11 and some receivers like FZD2, 4 and 10. In addition, increase in protocadherin-PC also leads to differentiation of the LNCaP cells to cells of neuroendocrine phenotype. This transdifferentiation induced by the protocadherin-PC is abolished when the neoplastic cells are treated with anti-β-catenin siRNA or with a anti-LEF antisense vector showing thus, that this process of transdifferentiation is an associated activation of the Wnt pathway [6]. In conclusion, experimental studies show the implication of the protocadherin-PC in the progression of the prostate cancer. Thus, this protein represents a target for the treatment of this malignancy.

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