

Implication of gelatinases in retinoblastoma development

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Abstract

The aim of this paper was to reveal the latest clinical and research findings regarding the implications of MMP2 and MMP9 matrix metalloproteinases in retinoblastoma development. The targets were finding better options for the therapeutic approach, considering the etiopathogeny and biology of this tumor.

Keywords: retinoblastoma, gelatinases

Retinoblastoma is a frequent malignant tumor of childhood and is developed from immature cells of the retina. It is the most common cancer with an incidence rate of 1/ 15.000 -1/ 28.000 [1] which decreases with age, becoming very rare in young children.

Retinoblastoma may be hereditary, in which case the disease afflicting both eyes but can also show other forms of pathogeny, in relation with the congenital mutations of a 13th chromosome gene (commonly unilateral forms). The tumor's clinical size and number may vary. Trilateral retinoblastoma in which the pineal gland, suprasellar and parasellar region were involved, was also described.

Several studies demonstrated neoangiogenic capacity, correlated with local invasion and metastasis [2].

The vital prognostic was good in most children but with possible sacrifice of their vision, eye removal being sometimes necessary.

Matrix metalloproteinases are zinc-dependent enzymes involved in the local invasion and migration of tumor malignant cells, through

their properties to degrade protein components of the basal cell membrane and extracellular matrix. Gelatinases A and B degrade gelatin and type IV, V, VI, X collagens, factors with an important role in the adherence between cells and matrix [3,4].

Several studies proved the ability of retinoblastoma cells to generate gelatinases, a fact related to neovascularization, hyperplasia, and differentiation. Findings showed that the expression of MMP-2 and MMP-9 is higher in aggressive tumors with extraocular extension and optic nerve invasion (tumoral grade III and IV) [5,6]. Also, the prognosis of retinoblastoma is significantly related to the optic nerve invasion and clinical stage of the disease.

The biological behavior of MMP-2 and MMP-9 allows the establishing of targets for cancer treatment by means of inhibiting their expression and blocking their activity [1].

A clinical study using a mouse model for retinoblastoma has focused on developing adjuvant therapies useful in controlling the local invasion and in reducing toxicity, if systemic chemotherapy was used. Due to the angiogenic

capacity of the tumor cells, the local invasion and metastasis was controlled by using vessel-targeting drugs like antiangiogenic agents as anecortave acetate (AA) and glycolytic inhibitors such as 2-deoxy-D-glucose. The results proved that a single subconjunctival injection with AA inhibits the upregulation of MMP-2 and MMP-9 in retinoblastoma cells in mice. The assessment of the angiogenesis process also showed that gelatinases degrade the extracellular matrix, allowing the release of angiogenic and other growth factors (components of cellular matrix). The angiogenic factors in turn, also increased the local accumulation of gelatinases and urokinase plasminogen activator (u-PA), which facilitated the destruction of the basal lamina and created gaps that allowed the neovessels development. The urokinase plasminogen activator leads to plasminogen mediated conversion of proMMPs (the inactive form of metalloproteinases) to active MMPs. The results of the study elicited that u-PA is indirectly inhibited by AA. Also, AA directly inhibits gelatinase transcription in mice retinoblastoma cells [7].

The assessment of 92 kDa type IV collagenase gene expression in retinoblastoma cells demonstrated a regulating mechanism of gene expression independent from the pathway triggered by inflammatory cytokines [8]. Binding proteins from retinoblastoma cells (Sp1 family proteins) can link specifically to and up-regulate the expression of MMPs, that can otherwise be regulated by cytokines and tumor promoters like TNF α , EGF, IL1, and TPA through binding the AP1 site [9]. Findings showed that the transcription of MMP-9 promoter was stimulated by TNF α through its binding to NF-kB and sp1. The expression of v-Src also induces the synthesis of MMP-9, mediated by the alteration of binding factors such as AP-1 and GT-box (homologous to the retinoblastoma control element), showing a different pathway to induce the synthesis of MMP-9.

The GT box can produce an anti-oncogene or a tumor suppressor gene product [10,11]. The retinoblastoma control element (RCE) regulates the transcription of c-fos, c-myc and TGF β 1 promoters. In conclusion, the alteration in the matrix protein synthesis/ metabolism plays an important role in tumor metastasis through the role of the GT box homologous to RCE (retinoblastoma control element), through the

regulation of genes related to MMP-9 [8].

Hypoxia is one factor that determines the therapeutic response in retinoblastoma [12,13] and is related to the invasion of the choroid, optic nerve, orbit tissue and distant metastasis [14,15].

The hypoxic environment activates the overexpression of the NF-kB factor that contributes to tumor cells biological behavior changes (like adhesive and invasive abilities). The expression of MMP-2, MMP-9 and VEGF is significantly elevated by the oxidative stress stimulation and by the overexpression of NF-kB [16].

The clinical trials assess the therapy targeting numerous genes implicated into the etiology of retinoblastoma. The aim of one study was to define the impact of SUZ 12 (an important component of the polycomb group protein PcG) in the gene expression alteration. SUZ 12 regulates tumor phenotype, thus tissue cell proliferation, cell cycle and embryonic development process via the gene promoters control. According to this clinical evidence, SUZ can reduce MMP-2, MMP-9 and VEGF activity [17].

In conclusion, the matrix metalloproteinases 2 and 9, also known as type IV gelatinases, are key enzymes in the degradation of extracellular matrix, and are therefore associated with tumor growth, neoplastic cell invasion, and metastasis. Being intimately implicated in cancer mechanisms, they are a potential target for future therapy and may also be a prognostic marker, or a monitor for the tumor follow-up.

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