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Rb family proteins in gastric cancer (Review)

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Abstract. Gastric cancer is one of the most diffuse neoplastic pathologies in the world whose environmental and molecular causes, although deeply investigated, have not been completely clarified. Besides some well-established etiological factors, such as *Helicobacter pylori* and E-cadherin mutations, investigations on other possible causes gave contrasting results. Rb family proteins (including pRb/p105, pRb2/p130 and p107) are involved in cell cycle regulation and their function and/or expression is often lost in various kinds of tumours such as lung, bladder, breast and brain cancer. The consequences of RB inactivation in tumours can be very different depending on the context and the type of cancer. Recent evidence indicates that Rb status correlates with a different therapeutic response according to the tumour type and the therapeutic agent. Studies performed on Rb family proteins in gastrointestinal tract tumours suggest that these proteins have an important role in these cancer types. However, owing to contrasting results, further investigation is required to assess whether the expression of Rb family proteins can potentially be used as a prognostic or predictive factor in gastric cancer.

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1. Introduction

Gastric cancer is one of the most frequent causes of cancer death in the world, even though in the past few years there has been a marked decrease in incidence in Western countries (1-3), whereas positive and negative trends are reported in Middle and Far East (4-7).

The most used histotype classification of gastric cancer is, according to Lauren (8), who defined a 'diffuse phenotype' characterized by diffuse infiltration of single tumour cells or grouped in nests, and an 'intestinal phenotype' showing similarity with histological features of differentiated intestinal carcinoma. More recently, gastric cancers showing characteristics of both histotypes were classified as 'mixed' (9). The intestinal histotype progresses through different steps beginning with atrophic gastritis to intestinal metaplasia, dysplasia, carcinoma and subsequent metastasis.

Investigations on the etiological factors related to the environment, above all to a diet rich in calories, high salted and smoked food, so as the possible protective role of fresh fruit and vegetables, gave contrasting results (10-14). However, the country of birth seems to be an established predisposing factor. Gastric cancer, in fact, is more diffuse in some parts of the world such as Japan, China and Colombia (15), and studies performed on migrants showed that gastric cancer incidence decreases in descendants of Japanese migrants, suggesting that the environment plays an important part (16). Another well characterized predisposing factor is represented by *Helicobacter pylori* infection, which is able to cause gastritis with mucosal damage and increased regenerative proliferation (17,18) and whose infection increases 2 or 3 folds the possibility of gastric cancer occurrence (19). There is universal agreement in considering patients infected by *H. pylori* at high risk of developing gastric cancer (20).

So far, just few biomarkers have been well characterized in their involvement in gastric cancer development. E-cadherin (epithelial cadherin, or CDH1-cadherin 1) is a calcium dependent cell-cell adhesion glycoprotein the loss of which contributes to cancer progression by increasing proliferation, invasion and metastasis. Point mutations and/or promoter hypermethylation of E-cadherin gene causing loss of function and/or expression of the related protein were described by different authors (21-24). RUNX3 (runt-related transcription factor 3) is a transcription factor acting as an oncosuppressor

the function of which is often lost in gastric cancer because of cytoplasmic delocalization, promoter hypermethylation and gene mutations (25-27). RUNX3 is involved in the apoptotic pathway triggered by TGF-ß1 (27) and it is considered a crucial therapeutic target in gastric cancer (28).

Among oncosuppressors lost in gastric cancer, various attempts are still ongoing to define the role of pRb family, comprising three members, all involved in cell cycle regulation, named pRb/p105, pRb2/p130 and p107 (29-31). They are also called 'pocket proteins' because they all have a pocket domain that allows them to bind E2F transcription factors and thereby block cell cycle progression (32). Particularly pRb/p105 binds E2F1, E2F2 and E2F3, whereas pRb2/p130 and p107 bind E2F4 and E2F5 (33). They also share the capability of binding histone deacetylase 1 (HDAC1) that cooperates with pocket proteins in binding and repressing E2Fs (32).

E2Fs activate transcription of several target genes among which *cyclin A2*, *CDC2, CDC6* and *MAD2* whose roles are related to cell cycle progression, apoptosis and DNA replication (34-36).

During quiescence, pocket proteins are hypophosphorylated: in this 'active' state they bind E2Fs determining inhibition of their transcription activity. After mitogenic stimuli D-type cyclin synthesis occurs and the subsequent formation of complexes between cyclins D and cyclin dependent kinases (CDK) 4 and 6 (37) induces pocket protein phosphorylation, and the consequent release of E2Fs that are free to activate the transcription of their target genes required for progression through the cell cycle.

Consistent with the importance of Rb in controlling cell proliferation, mutations in Rb or its pathway are extremely common in most cancer types.

However, beyond their role in regulating cell cycle progression through the binding to E2F factors, in the past decades numerous studies implicated Rb family proteins in many cellular processes that could all contribute to their tumour suppressor function, suggesting that the role of Rb in cancer is more complex than previously thought (38). Moreover, Rb inactivation in tumours can have different effects depending on the context and the type of cancer. Recent evidence indicates that Rb status can influence the response to different anti-cancer therapeutics according to the context, therefore, a thorough understanding of Rb function in different cancer types is pivotal (39). So far, pocket protein involvement in gastric cancer development is quite controversial since scarce data exist on pRb2/p130 and p107 role in this tumour type (40-42) and contrasting data on pRb/p105 expression levels are reported (43,44). Here, we summarize what has been found so far on the role of pocket proteins in the development of gastric cancer. More efforts will be necessary, however, to clarify whether Rb family status can serve as a prognostic or predictive factor and help in the future clinical management of this disease.

2. pRb/p105

pRb/p105 (also known as Rb1, RB or pRb) takes its name from retinoblastoma, a tumour of the retina arising in childhood, determined by two distinct mutations at *pRb/p105* locus, each causing loss of function of one of the two homologous copies (45).

pRb/p105 is located on chromosome 13q14.2 and mutations to this locus were first found in small and non-small cell lung carcinomas (SCLC and NSCLC), bladder carcinomas and sarcomas (28,46). Indeed, pRb/p105 is frequently mutated in a variety of human cancers, both directly, through different mechanisms, and indirectly, through deregulation of other pathway members. For example, Rb loss of function can be caused by deregulation of upstream control pathways (47) or owing to viral oncoproteins (48). Adenovirus E1A protein, Simian Virus 40 tumor antigen (T antigen), and Human Papillomavirus E7 protein share the capability of disrupting the interaction between E2F and the retinoblastoma gene product (49-52). Although the above-mentioned viruses are evolutionarily distinct, their transforming proteins share some similarities in their amino acid sequence (52), which allow them to impair the interaction between pRb/p105 and E2F, determining E2F release and activation of its transcriptional targets.

In normal cells, during G0 phase, hypophosphorylated pRb/p105 binds E2F1, E2F2 and E2F3 inhibiting their activity. Upon mitogenic stimuli, pRb/p105 phosphorylation induced by cyclin D/CDK4/6 complexes causes E2F release (53), during the early G1 phase. To allow further cell cycle progression mitogenic stimuli must remain at least until middle-late G1, so that cells reach the restriction (R) point representing the key event in deciding whether halting or proceeding through the cycle (54). pRb/p105 exerts a pivotal role in this G1/S transition (51,55,56). Then, to guarantee E2F activity, pRb/p105 will be maintained hyperphosphorylated by the cyclin E/CDK2 complexes throughout the other cell cycle phases (56).

pRb/p105 allows cells to control G1/S transition and when this function is lost because of mutations, promoter methylation and subsequent gene silencing, hyperphosphorylation or increased degradation, cells can grow in spite of possible other pathway malfunctions and/or DNA damage (57-59).

3. pRb/p105 in gastric cancer

Mutations affecting pRb/p105 function or its pathway occur in most tumour types (60). Usually, pRb/p105 loss of function determines uncontrolled cell cycle progression and increase of genomic instability that favours tumorigenesis (61,62). However the pRb/p105 role in gastric cancer is not as clear as in other tumours, owing to some controversial data. In 1996 Songun *et al* (43) found a connection between pRb/p105 expression and lymph node metastasis. They noted that there was a direct correlation between TNM stage and pRb/p105 expression. In particular, they studied 105 cases of primary gastric adenocarcinoma in which they analyzed pRb/p105 expression by immunohistochemistry. They found that pRb/p105 expression was higher in T4 stage and in TNM stage 4 samples. Similar results were described by Arici *et al* (63) who found a higher expression rate of pRb/p105 and cyclin D1 in gastric cancer samples, compared with adjacent non-neoplastic mucosa. These data are quite surprising considering that pRb/p105 is the prototype onco-suppressor

ierally lost in tumours (64,65). In 1999 Coppola *et al* yzed by immunohistochemistry the expression of pRb/p105 in 56 gastric cancers arisen in patients suffering from Barrett oesophagus. Barrett oesophagus is a predisposing factor for the so-called 'cardiac' cancers, which are tumours of the stomach cardias and distal oesophagus junction. Cardiac cancers arise through a stepwise process termed the metaplasia-dysplasia-carcinoma sequence (66), which often starts with Barrett oesophagus in which columnar epithelium replaces the squamous epithelium that normally lines the distal oesophagus (67). This replacement represents a form of incomplete intestinal metaplasia, called 'specialized intestinal metaplasia', predisposing patients to adenocarcinoma (67). So, the analysis by Coppola *et al* considers different steps of progression from Barrett oesophagus to gastric cancer. Their results showed a progressive reduction of the pRb/p105 level from normal tissue to progressive stages of metaplasia, dysplasia, until gastric cancer and this is more consistent with the expectations based on the pRb/p105 role in tumour development (68,69).

These seemingly contrasting results could be explained by the fact that the high levels of pRb/p105 found by Arici *et al* could concern an inactive protein. pRb/p105, in fact, might be inactivated because of hyperphosphorylation (60,70) or because of gene mutations (71,72), which were not assessed.

Contrasting data were found also when analyzing pRb/p105 mRNA levels. In 1998, Chen *et al* reported a lower level of pRb/p105 mRNA in gastric cancer, compared with non-cancerous tissue samples. Similar data were found by others in different tumour types (73,74). Decreased transcription of *pRb/p105* may be due to promoter hypermethylation or LOH (75). By contrast, in 2003 Lan *et al* (76) found Rb/p105 mRNA upregulation in gastric cancer. They compared 272 cases of patients suffering from chronic gastritis, intestinal metaplasia type I, II and III (IMI, IMII and IMIII), mild and moderate dysplasia (DysI and DysII), severe dysplasia (DysIII) and gastric cancer. They found a progressive increase of pRb/p105 mRNA level from the mildest to the worst stage of the illness and correlation between high pRb/p105 mRNA level and gastric cancer was even stronger in cases from patients infected with *H. pylori*. De Luca *et al* (77) demonstrated that CagA and HspB proteins produced by *H. pylori*, can contribute to increase pRb/p105 phosphorylation via cyclin D3 increased expression. So, it can be supposed that presence of *H. pylori* may contribute to hyperphosphorylation and consequent loss of function of pRb/p105 protein. Therefore, pRb/p105 high mRNA level could be due to an attempt of the cell to compensate its loss.

Interestingly, a recent study describes the effects of an indole derivative produced in stomach after consumption of crouciferous vegetables (78). The authors show a decrease in CDK2 activity with a consequent reduction of pRb/p105 hyperphosphorylation and cell cycle arrest in a colon carcinoma cell line demonstrating a direct effect exerted by pRb/p105 in blocking cell cycle progression in an *in vitro* model of gastrointestinal cancer.

In a recent study Guo *et al* analyzed miRNA expression profiles in gastric cancer samples and they found that miR-106, which targets pRb/p105 mRNA, is upregulated in gastric cancer specimens, comparing with adjacent non-neoplastic tissues. Consistent with this result, immunohistochemistry performed on the same samples showed a decreased pRb/p105 expression in gastric cancer compared with the normal specimens (79). This study suggests that other molecular mechanisms exist to govern pRb/p105 mRNA and protein expression, which might be altered in gastric cancer, adding another layer to the complexity of pRb/p105 regulation.

4. pRb2/p130

pRb2/p130 was cloned in 1993 by Mayol *et al* and is located on chromosome 16q12.2 (80,81). The activity of pRb2/p130 is regulated by phosphorylation by cyclin D/CDK4/6 and cyclin E/CDK /2 complexes (82-84), and GSK3 (Glycogen Syntase kinase 3) (85). Cyclin D/CDK 4/6 complexes are active during early G1 phase and cyclin E/CDK2 during G1/S transition, whereas GSK3 phosphorylates pRb2/p130 during G0 phase contributing to increase protein stability. pRb2/p130 is the only pocket protein phosphorylated in G0 (82,86) and in terminally differentiated cells and animal tissues (87). During quiescence state pRb2/p130 binds the E2F4 and E2F5 transcription factors inhibiting transcription of their target genes such as cyclin A2, CDC2 and CDC6, all involved in cell cycle progression and neoplastic transformation (88-90).

pRb2/p130 function is lost in several kinds of tumours such as glioma, lung cancer, Burkitt lymphoma, ovarian carcinoma and breast cancer (91-95). pRb2/p130 loss of function occurs because of mutations, promoter hypermethylation, increased degradation, or interaction with viral proteins (96-100). These events may cause synthesis of inactive protein, gene silencing, decreased protein amount or protein inactivation. Loss of pRb2/p130 causes the release of E2F4 and E2F5 which are then free to activate transcription of their target genes promoting cell cycle progression.

Some exceptions, however, have been found. In hepatocellular carcinoma, for example, Huynh (101) found overexpression of pRb2/p130 also in tumour tissue and in adjacent benign liver. Interestingly, he found both cytoplasmic and nuclear expression by Western blot analysis, whereas a decreased expression or a prevailing citoplasmic localization was expected. However, transfecting HepG2 (human hepatocellular carcinoma cell line) with *pRb2/p130* cDNA determined an increased number of cells in G0/G1 phase and a reduced tumour burden in SCID mice, compared with untransfected HepG2. Thus, pRb2/p130 acts as oncosuppressor in hepatocellular carcinoma and it might be that its overexpression in tissue samples could be an attempt of cells to activate a protective response against uncontrolled growth.

5. pRb2/p130 in gastric cancer

The role of pRb2/p130 in gastric cancer has not been thoroughly investigated. Mattioli *et al* (40) did not find striking evidence of direct correlations between gastric tumour progression and protein expression. The most important result that they found was a high cytoplasmic staining along with a high nuclear localization as well, in gastric cancer with intestinal histotype, whereas a correlation was not found with the diffuse histotype.

In 1999, Yoo *et al* (42) found that TGF-ß1 treatment of the human gastric carcinoma cell line, SNU-16, determined cell cycle arrest in G1/S by enhancing the cell cycle inhibitor p21WAF1/CIP1 and subsequent inhibition of cyclin D/CDK4/6 and cyclin E/CDK2 complexes associated with their respective CDKs. This led to decreased phosphorylation of pRb2/p130 which can be considered a downstream target of TGF-ß1 pathway and whose deregulation may be involved in gastric cancer development.

Although these data show that pRb2/p130 deregulation may be involved in gastric cancer, further research is necessary to support a direct role. It may be useful, for example, investigating whether point mutations in *pRb2/p130* occur (97,102) or whether the protein is hyperphosphorylated by the cyclinD-E/CDK2/4/6 complexes (103) or inactivated through other mechanisms.

6. p107

p107 was cloned in 1991 by Ewen *et al* (104) and maps on chromosome 20q11.2. P107 protein shares with pRb/p105 and pRb2/p130 the capability of binding E2Fs through its pocket domain. It binds E2F4 and E2F5 (104-108) but it is also able to interact physically with the cyclin E/CDK2 and cyclin A/CDK 2 complexes through its pocket spacer domain (109). Knockout mice for p107 show normal phenotype, whereas double knockouts $p107^{-/-}$; $pRb2/p130^{-/-}$ show defects above all in limb development and double knockout $p107^{-/-}$; $pRb/p105^{-/-}$ have a phenotype that strongly resembles $pRb/p105^{-/-}$ and a shorter lifespan (108,110,111).

In its role in controlling cell cycle Xiao *et al* (112) showed that p107 is phosphorylated by cyclin D/CDK4/6 starting from mid G1 and proceeding through late G1 and then S phase although a role of cyclin E/CDK2 and cyclin A/CDK2 cannot be excluded. It has been shown that p107 can act as a direct inhibitor of cyclin A-E /CDK2 complexes, rather than a simple substrate (113).

The role of p107 in tumour development is not well defined. In 1993 Zhu *et al* (31) showed that p107 has growth suppressive properties. In fact, p107 forced expression in two human osteosarcoma cell lines, SAOS-2 and U2OS, inhibited cell proliferation. But, as the authors themselves underline, cell growth arrest properties are not necessarily indicative of tumour suppressive properties. They mention Brookstein *et al* (114) who showed that reintroduction of wild-type *pRb/p105* in the DU145 prostate carcinoma cell line inhibits tumour formation in nude mice, although it does not affect cellular growth rate. Wu *et al* (115) found that in colorectal cancer p107 is progressively increased tissue until the stage of early carcinoma whereas its level rapidly decreases in liver metastasis, lymphatic invasion and advanced stage, suggesting that p107 oncosuppressor activity is more evident in the late stages of tumour development. Moreover, studies on double knockout mice $pRb/p105^{-/-}$; $p107^{-/-}$ suggested that loss of p107 aggravates the phenotypic consequences of epidermal-specific deletion of pRb (116). Santos *et al* also showed that mice lacking both pRb/p105 and p107, but not pRb/p105 alone, developed spontaneous skin tumours and that the deficiency of both makes them highly susceptible to Ha-ras transformation (117,118).

Contrasting data were recently found by a dissociable antibody microarray (DAMA), a technique that combines protein microarrays with traditional immunostaining, on normal and cancer breast cell lines showing that p107 is one of the upregulated proteins in cancer compared to normal cells (119). Data were confirmed by Western blot analysis and statistical analysis leading the authors to consider p107 a candidate biomarker for breast cancer diagnosis. Nevertheless, it has been shown that in DU145 depletion of p107 inhibits senescence induced by p53 dependent-DNA damage response, suggesting that p107 loss could underlie tumour development (120).

These seemingly contrasting results could be explained by the fact that p107 function is highly dependent on the context. For example, despite binding the same E2F transcription factors, E2F4 and E2F5, p107 and pRb2/p130 do not have a redundant role in tumorigenesis. Rather, the requirement for pocket proteins in tumour suppression seems to be cell-type dependent as shown by the fact that $pRb/p105^{-/-}$; $p107^{-/-}$ and $pRb/p105^{-/-}$; $pRb2/p130^{-/-}$ mice do not have an overlapping tumour spectrum (116). In retina, for example, both pRb2/p130 and p107 are necessary to suppress proliferation of $pRb/p105^{-/-}$ cells, whereas in the adrenal gland loss of pRb/p105 can be compensated just by pRb2/p130. Indeed, osteosarcomas occur in $pRb/p105^{+/-}$; $p107^{-/-}$ and not in $pRb/p105^{+/-}$; $pRb2/p130^{-/-}$ mice (121). Substantially, p107 role in cancer development may be highly related to cell type and this may explain the contrasting results found in different kinds of tumours. Further investigations will help to define the role of each pocket protein and to identify both common and specific pathways.

7. p107 in gastric cancer

So far, only two studies have been published investigating p107 role in gastric cancer. In 1996, Wang *et al* (122) described a different effect of staurosporin, a protein kinase inhibitor, on the human gastric adenocarcinoma cell line, BGC-823, compared to the normal 2BS cell line. Staurosporin blocked in G1 phase the normal cell line through reduction of calmodulin and calcium ions and a decrease of p107 phosphorylation. In the cancer cell line, instead, staurosporin induced calmodulin decrease and calcium ion increase and consequent loss of the G1 phase arrest, suggesting that p107 phosphorylation could be a downstream target of the ion equilibrium in gastric environment, whose loss could underlie tumorigenesis.

A more recent study concerns the interaction between p107 and the regulatory subunit p55γ of PI3K (41). Here, the authors investigated the effects exerted by p55γ on the MKN-28 human gastric cell line. Forced expression of the 24-amino acid N-terminal end of p55γ determined a block of cell cycle in G1 phase, inhibition of DNA synthesis and down-regulation of cyclins D and A expression. They found that p55γ binds both pRb2/p130 and p107 and they speculated that this binding may affect pocket proteins interaction with E2F factors modifying downstream pathways. Besides, since both cyclins D and A complexed with respective CDKs are involved in pocket protein phosphorylation, their reduction may contribute to G1 arrest because of reduction of pRb2/-

p107 phosphorylation. Although the role of p55γ in with pocket proteins deserves further investigation, this study casts light on the importance of p107 in gastric cancer development.

8. Conclusion

The small family of pocket proteins including pRb/p105, pRb2/p130 and p107 exerts a pivotal role in the control of cell cycle progression (53,82,86,123). However, dissecting the precise role of pocket proteins is complicated not only because they have both overlapping and distinct functions but also because they are involved in almost all biological processes. Moreover, they regulate the transcription of a myriad of target genes, both by up- and down-regulation and can interact with many other cellular proteins. For example, they are able to form complexes (32,124,125) which help them to repress E2F activity and with other molecules such as MyoD (126) involving pRb/p105 in muscle differentiation, and Raf-1 (130), which is able to inactivate E2F interaction with pRb/p105 and pRb2/p130.

Consistent with their oncosuppressor functions, pocket proteins are often dysregulated in a variety of tumours (128-132). Generally, hyperphosphorylation, point mutations or protein delocalization lead pocket proteins not to bind their respective E2F partners thereby promoting unscheduled cell cycle progression. However, it is likely that also other molecular mechanisms, which have been previously overlooked, can affect Rb family function in cancer, such as for example post-transcriptional regulation by microRNAs. In gastric cancer, however, more investigations are necessary to clarify the status and function of the three pocket proteins. This seems particularly crucial as it has been recently shown that pRb/p105 status can be predictive of the therapeutic response to different anti-cancer agents according to the context. Up to date, loss of function of pRb/p105 seems to be a more common event in gastric cancer, however, a deeper analysis of the cases showing pRb/p105 upregulation should help to clarify its role in these tumours. It will be equally important, to investigate further the pRb2/p130 and p107 function in gastric cancer, since the data discussed here point to a role of these proteins in gastric cancer development.

Despite ongoing efforts, a definitive standard chemotherapy regimen for gastric cancer has not been defined yet and surgery often remains the first choice of treatment. Several studies are ongoing to establish the utility of preoperative and postoperative chemotherapy although it is crucial to find novel biomarkers that could help to identify the more appropriate therapeutic regimen. Considering the emerging role of pocket proteins as possible predictive factors of tumour outcome it seems urgent to better define their role in gastric cancer and assess whether they could represent a potential useful tool for the clinical management of gastric cancer patients.

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