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High mobility group protein HMGI-C: a molecular target in solid tumor formation

Review Article

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Summary

The high mobility group protein HMGI-C is a non-histone chromosomal protein characterized by its capacity to bind in the narrow minor groove of AT-rich DNA. It is thought to act as a so-called architectural transcription factor and to modulate the expression of target genes through the formation of stereospecific complexes on the regulatory regions of these targets. Towards defining its function, there is now increasing evidence for a critical role of HMGI-C in the regulation of cell growth and proliferation. A direct role for HMGI-C in tumorigenesis has been demonstrated by the finding that the *HMGI-C* gene on human chromosome 12q15, is rearranged in a variety of solid tumors, resulting in ectopic expression. In lipomas, the *LPP* gene on chromosome 3q27-28 is the preferential translocation partner. It was shown to encode a novel, proline-rich, LIM domain containing protein and HMGI-C/LPP fusion transcripts have been identified in lipomas. Moreover, in overexpression experiments, the tumor-derived aberrant HMGI-C protein products are able to induce neoplastic transformation. In complementary studies, it was shown that targeted inactivation of *Hmgi-c* in mice disrupts both pre- and postnatal growth, resulting in the *pygmy* phenotype. When cultured *in vitro*, pygmy mouse-derived embryonic fibroblasts display a lower growth rate. In addition, anti-sense *HMGI-C* expression has been shown to inhibit retrovirally induced transformation.

I. Introduction. Chromosome 12q13-15 rearrangements in solid tumors

Rearrangements involving chromosome region 12q13-q15 are associated with a wide variety of human solid tumors, both malignant and benign. Among benign neoplasms, these recurrent chromosomal aberrations are observed in e.g. uterine leiomyomas (smooth muscle) (Heim et al., 1988; Vanni and Lecca, 1988), endometrial polyps (Walter et al, 1989; Vanni et al., 1993), lipomas (Sreekantaiah et al, 1991) pleiomorphic adenomas of the salivary glands (Bullerdiek et al, 1993), pulmonary chondroid hamartomas (Kazmierczak et al., 1995a), and fibroadenomas of the breast (Staats et al., 1996). Malignant tumors involve liposarcomas (Berner et al, 1997), osteosarcomas (Kools and van de Ven, 1996; Berner et al., 1997), and aggressive angiomyxomas (Kazmierczak et al., 1995). The clinical relevance is maybe best illustrated by the fact that uterine leiomyoma is the most common pelvic neoplasm in women, occurring with an incidence of up to 77% of all women of reproductive age. Although most patients with these steroid-dependent tumors (Kawaguchi, 1989 and references therein) are asymptomatic, leiomyomas can be associated with abnormal uterine bleeding, pelvic pain, urinary dysfunction, spontaneous abortions, premature delivery, and infertility (Quade, 1995). The high incidence of this benign smooth muscle tumor constitutes a major public

health problem, leading to over 200,000 hysterectomies performed annually in the USA, on the basis of the diagnosis of myomatous uterus (Cramer 1990; Carlson, 1993).

The above-mentioned anomalies of chromosome 12 segment q13-15 seem to be one of the most frequent chromosomal abnormalities associated with mesenchymal neoplasms in humans. Recently, it has been shown that the *HMGI-C* gene is affected by these chromosomal aberrations (Ashar et al., 1995; Schoenmakers et al., 1995; Kazmierczak et al., 1996). The structure of the human *HMGI-C* gene and its protein product is shown in **Figure 1** and will be discussed in more detail in one of the next sections. The gene consists of five exons and spans about 175 kb of genomic DNA. Many breakpoints were found to be clustered within the large (>140 kb) third intron, resulting in the loss of exons 4 and 5. By means of RT-PCR analysis, we have shown that the corresponding transcripts encode a truncated version of the HMGI-C protein in which the carboxy-terminal domains are deleted. In addition, some breakpoints were found in the 5'- and 3'-flanking regions of the *HMGI-C* gene. In lipomas and osteosarcomas a specific amplification of a rearranged *HMGI-C* gene was detected, resulting in ectopic expression of *HMGI-C* (Kools and van de Ven, 1996; Berner et al., 1997). Many chromosomes have been found as translocation partner of *HMGI-C*. By means of RT-PCR analysis, various aberrant fusion transcripts were detected (Schoenmakers, 1997). So far, only a few fusion partner genes of *HMGI-C* have been extensively characterized, i.e. the *FHIT* (Geurts et al., 1998) and *NFIB* (Geurts et al., 1997) genes in pleomorphic adenomas of the salivary glands, the mitochondrial aldehyde dehydrogenase gene (*ALDH2*) in a uterine leiomyoma (Kazmierczak et al., 1995b). Moreover, this review will discuss recent data on the preferential translocation partner genes on chromosomes 3q27-28 in lipomas (Turc-Carel et al., 1986) and 14q23-24 in uterine leiomyomas (Mitelman, 1991).

In lipomas, we have identified and characterized the chromosome 3-derived translocation partner gene of *HMGI-C*, which we have designated *LPP* (Lipoma Preferred Partner gene) (Petit et al., 1996, 1998). We were able to detect aberrant transcripts encoding HMGI-C/LPP fusion proteins in both primary lipomas and lipoma cell lines. Apart from lipomas, *HMGI-C/LPP* fusion transcripts were also recently detected in a cytogenetic subgroup of pulmonary chondroid hamartomas with chromosome (3;12)(q27;q14-15) translocations (Rogalla et al, 1998). A detailed description of the resultant chimeric proteins and wild-type LPP will be provided in one of the next sections.

Only very recently, we have been able to molecularly define the uterine leiomyoma cluster region on chromosome 14q23-24 (ULCR14) to an interval of approximately 1 Mb. Subsequent gene-identification experiments within this region, revealed the presence of a single transcript, the exons of which are dispersed over an interval of approximately 0.9 Mb. FISH analysis of tumor-derived material revealed that all genomic breakpoints indeed mapped within the span of this gene. Furthermore, removal of the last exon seems to be the minimal tumor-associated event. By means of 3'-RACE and RT-PCR experiments we were able to confirm the direct, reciprocal involvement of this ULCR14 gene, since they led to the isolation of various HMGI-C-containing fusion transcripts (Schoenmakers et al., 1999).

II. The HMGI-C protein, DNA binding, and search for target genes

The HMGI-C protein belongs to the high mobility group (HMG) of DNA binding proteins. This class of nuclear proteins can be divided into three distinct families. The HMG-1/2, HMGI, and HMG14/17 families (reviewed in Bustin and Reeves, 1996). The HMGI family consists of HMGI-C, HMGI, and HMGY. The HMGI proteins are characterized by the presence of three DNA binding domains, the AT-hooks, containing a short stretch of basic amino acids, and a carboxy-terminal highly acidic domain. A prominent feature of these proteins is their ability to bind in the narrow minor groove of AT-rich DNA. HMGI and HMGY are derived by alternative splicing of transcripts of a single gene on chromosome 6p21 (Johnson et al., 1989; Friedman et al., 1993). Interestingly, the HMGI/Y gene was also found to be subject of chromosomal rearrangements in e.g. lipomas and pulmonary chondroid hamartomas (Kazmierczak et al., 1996; Tkachenko et al., 1997). In some cases, fusion transcripts and resultant chimeric proteins were detected. As is the case for HMGI-C, ectopic expression is observed in various tumor types (Ram et al., 1993; Tamimi et al., 1993).

The AT-hooks of HMGI-C are each encoded by separate exons (exons 1-3). Exons 4 and 5 encode the spacer domain and highly acidic carboxy-terminal tail, respectively, (**Figure 1**) and therefore translocations involving chromosomal breakage within intron 3, result in the synthesis of aberrant HMGI-C proteins in which the latter domains are deleted. Apart from an 11 amino acid segment only present within HMGI-C, the HMGI/Y and HMGI-C proteins display a high degree of sequence identity, especially within the three DNA-binding domains (**Figure 2**).

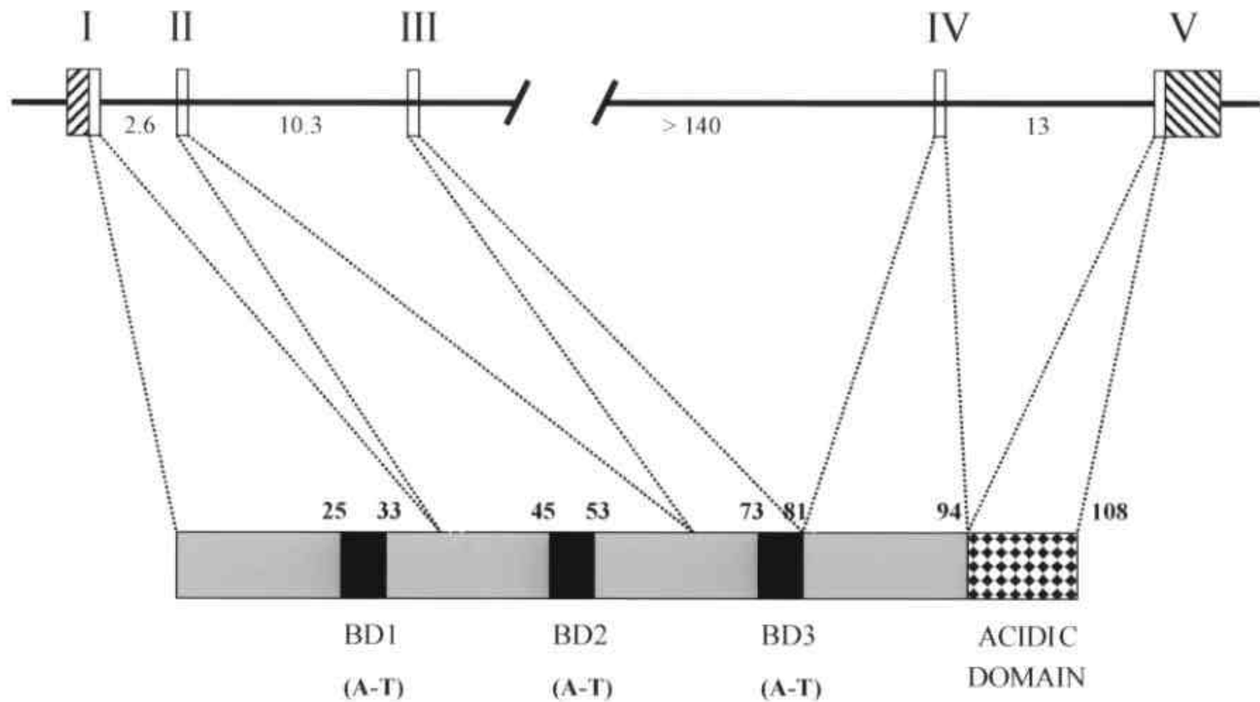

Figure 1. Structure of the human *HMGI-C* gene and its protein product. On the gene map, the exons are depicted as boxes, with the 5'- and 3'-unstranslated regions represented as shaded areas. The numbers below the map indicate the intron sizes in kb. The dashed lines indicate which regions of the HMGI-C protein are encoded by the individual exons and the amino acid numbering above the protein map mark the boundaries of the various DNA-binding and acidic domains.

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                                              BD1                                    BD2
I-C   (M) SARGEGAGQPSTSAQGQPAAPAPQKRGRGRPRKQQQ                   EPTGEPSPKRPRGRPKG
Y     (M) SESSSKSSQPLASKQEKDGT    EKRGRGRPRKQPP                 KEPSEVPTPKRPRGRPKG
I     (M) SESSSKSSQPLASKQEKDGT    EKRGRGRPRKQPPVSPGTALVGSQKEPSEVPTPKRPRGRPKG

                              BD3                      ACIDIC DOMAIN
I-C   SKNKSPSKAAQKKAEATGEKRPRGRPRKWPQQVVQKKPAQEETEETSSQESAEED
Y     SKNKGAAKT  RKTTTTPGRKPRGRPKK      LEK      EEEEGISQESSEEEQ
I     SKNKGAAKT  RKTTTTPGRKPRGRPKK      LEK      EEEEGISQESSEEEQ
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Figure 2. Human HMGI-C amino acid sequence aligned with human HMG-I and HMG-Y.

The overall structure of HMGI proteins is reminiscent of the modular structure of a classical transcription factor containing activation and/or silencing domain(s) spatially separated form the DNA binding domain (Sadowski et al., 1988). Therefore, in order to investigate whether HMGI-C could act as a classical transcription factor with activating and/or silencing properties, several domains of HMGI-C were fused to the DNA binding domain of the GAL4 protein and the resultant fusion proteins were assayed for transcriptional effects in a standard assay using chimeric

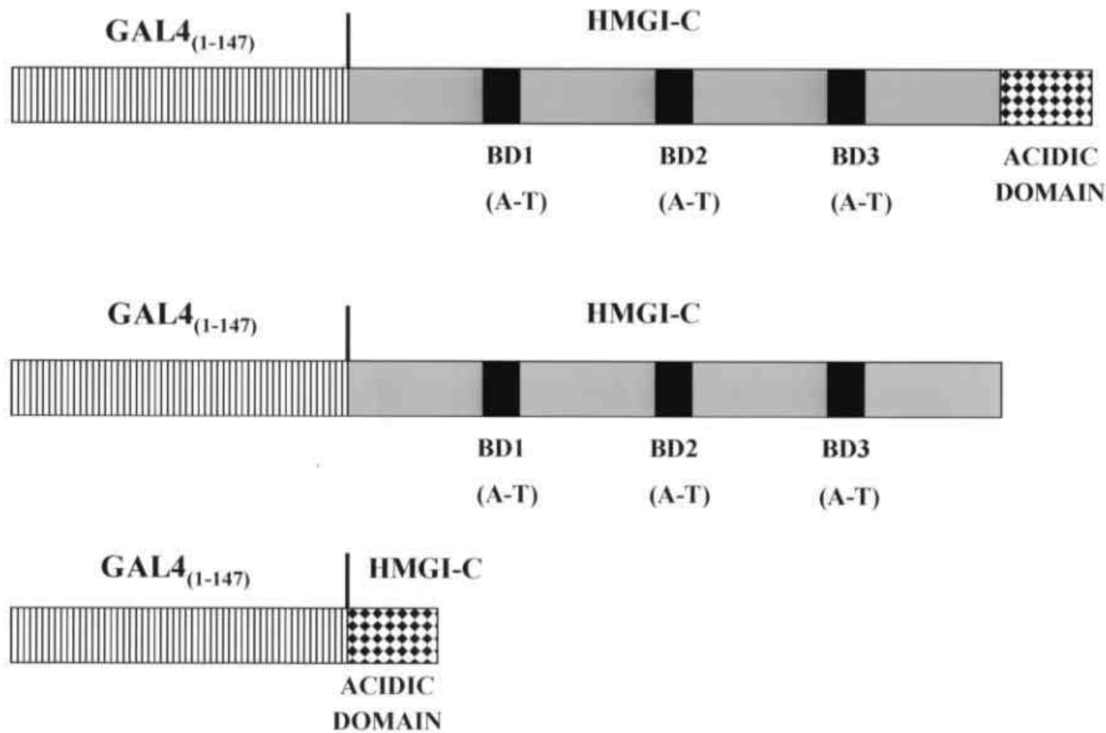

Figure 3. To investigate potential transcription activation or silencing activities associated with the HMGI-C protein itself, the various domains of it were fused to the DNA-binding domain of GAL4. In transfection experiments, we found no significant effect of the GAL4-HMGI-C hybrids on transcriptional activity of 5x-GAL4-luciferase reporter constructs.

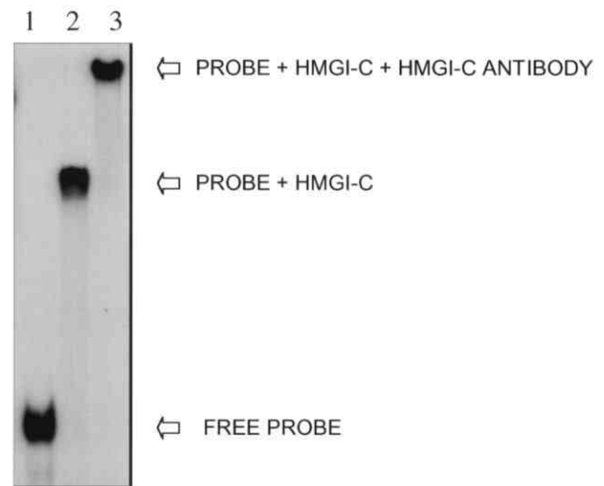

Figure 4. DNA binding activity of purified, recombinant human HMGI-C protein and its reactivity with anti-HMGI-C antibodies. In this EMSA experiment, a synthetic, double-stranded oligonucleotide containing high affinity binding sites was used as a probe. Lane 1, binding mixture with probe only, no HMGI-C added. Lane 2, 10 ng of HMGI-C added to the binding reaction. Lane 3, as lane 2, and anti-HMGI-C antibody also included. The antibody is raised against HMGI-C-specific amino acid residues. It does not interfere with DNA binding, but gives rise to a supershift of the existing protein-DNA complex.

promoter-luciferase reporter constructs containing GAL4 binding sites. As can be deduced from the results (**Figure 3**), both wild-type domains and the aberrant HMGI-C proteins as observed in tumors do not have transcription activating or silencing activities. These data are in agreement with the current model that the HMGI proteins do not regulate transcription on their own, but act in concert with other DNA binding proteins in order to specifically regulate target promoter activity. It is now believed that HMGI-C and HMGI/Y act as so-called architectural transcription factors (Wolffe, 1994) and thereby regulate the affinity and activity of other transcription factors by altering local chromatin structure. As a result of this, they modulate the expression of their

respective target genes through the formation of stereospecific complexes on the regulatory regions. This model is supported by experimental data of which the formation of a multi-protein complex, called "enhanceosome" at the interferon-ß promoter is most extensively described (Thanos and Maniatis, 1995; Yie et al., 1997). In addition, several other target genes for HMGI/Y have been identified in which HMGI/Y enhances or represses promoter activity (a detailed list is provided in Cmarik et al., 1998).

To aid the identification of HMGI-C target genes, of which none are known at the moment, we started with defining low and high affinity binding sites among all possible combinations of A/T-rich DNA stretches. This was done employing a PCR-assisted DNA binding site selection strategy (CASting) (Ko and Engel, 1993) using purified recombinant HMGI-C and anti-HMGI-C antibodies. DNA binding and antibody reactivity was evaluated in EMSA experiments (**Figure 4**). Preliminary results revealed a preference for homopolymeric A- or T-stretches, which were infrequently disrupted by C- or G-residues, respectively (Jansen et al., in prep). With the obtained set of data we are currently selecting potential target genes for transcriptional analysis. In addition, using a PCR-based subtractive cloning technique (Sagerström et al., 1997), we are in the process of isolating genes expressed in one cell population but not in another, e.g. *HMGI-C* knockout versus wild-type.

III. The HMGI-C/LPP fusion in lipomas

As mentioned above, we discovered the chromosome 3-derived translocation partner gene of *HMGI-C* in lipomas, which was designated *LPP* (Lipoma Preferred Partner gene). By Northern blot analysis, the *LPP* gene was shown to encode an mRNA of over 13 kb that is expressed in a variety of human tissues. We have constructed a cDNA contig encompassing the complete coding region of *LPP*. Nucleotide sequence analysis revealed that the gene encodes a novel protein of 612 amino acids that is unusually proline-rich, in its amino-terminal region, and has three LIM domains, in its carboxy-terminal region (Petit et al., 1996). LIM domains are cysteine-rich, zinc-binding protein sequences that are found in a growing number of proteins with diverse functions, including transcription regulators, proto-oncogene products, and adhesion plaque constituents. Many of the LIM family members have been postulated to play a role in cell signaling and control of cell fate during development and it was demonstrated that LIM domains can act as protein binding interfaces (Schmeichel and Beckerle, 1994).

Extensive studies on the genomic organization of the human *LPP* gene resulted in the identification of 11 *LPP* exons (dispersed over about 400 kb) with the predicted start codon in exon 3 and the stop codon in exon 11. All three LIM domains are encoded by separate exons. The function of LPP is not known, but database searches revealed that the LPP protein is a member of a new family of proteins. Apart from LPP, two other family members are known to date: TRIP6 and zyxin. TRIP6 was identified in a yeast two-hybrid assay as a Thyroid Receptor Interacting Protein (Yi et al., 1998). Zyxin (Beckerle, 1997), the founding member of this family, is found at sites of cell adhesion to the extracellular matrix (adhesion plaques), and was recently shown to enhance actin organizing activity in mammalian cells (Golsteyn et al., 1997). In addition, it was shown that this protein is able to shuttle to the nucleus (Nix and Beckerle, 1998).

Using RT-PCR in the analysis of a number of lipoma cell lines, primary lipomas, a parosteal lipoma, and pulmonary chondroid hamartoma, it appeared that *LPP* is frequently rearranged, also in cases without a cytogenetically detectable involvement of 3q27-28 (Petit et al., 1996, 1998; Rogalla et al., 1998). In lipomas, two alternative *HMGI-C/LPP* hybrid transcripts have been detected encoding the three DNA binding domains of HMGI-C followed by: 1) part of the proline rich domain and all three LIM domains of LPP or, most frequently observed: 2) the two most carboxy-terminal LIM domains (LIM 2-3) of LPP (**Figure 5**). The subcellular localization and transcriptional regulatory properties of wild-type LPP and the lipoma-derived HMGI-C/LPP fusion proteins are subject of present studies in our lab. This will provide further insight in the mechanism of lipoma formation.

IV. Critical role for HMGI-C in growth and development

There is now substantial evidence for the involvement of HMGI-C in the regulation of cell growth and proliferation. Moreover, as outlined above, a first clue came from the finding that translocations disrupting the human *HMGI-C* gene result in ectopic expression of *HMGI-C* in a variety of solid tumors (Ashar et al., 1995; Schoenmakers et al., 1995). A regulatory function of HMGI-C in growth and proliferation is further substantiated by the observation that targeted disruption of the *Hmgi-c* gene in mice results in a *pygmy* phenotype (Zhou et al., 1995). When cultured *in vitro*, pygmy mouse-derived embryonic fibroblasts display a lower growth rate (Zhou et al., 1995; and our unpublished observations). Interestingly, *Hmgi-c* inactivation does not affect the growth hormone/insulin-like growth factor endocrine pathway. In addition, anti-sense HMGI-C expres-

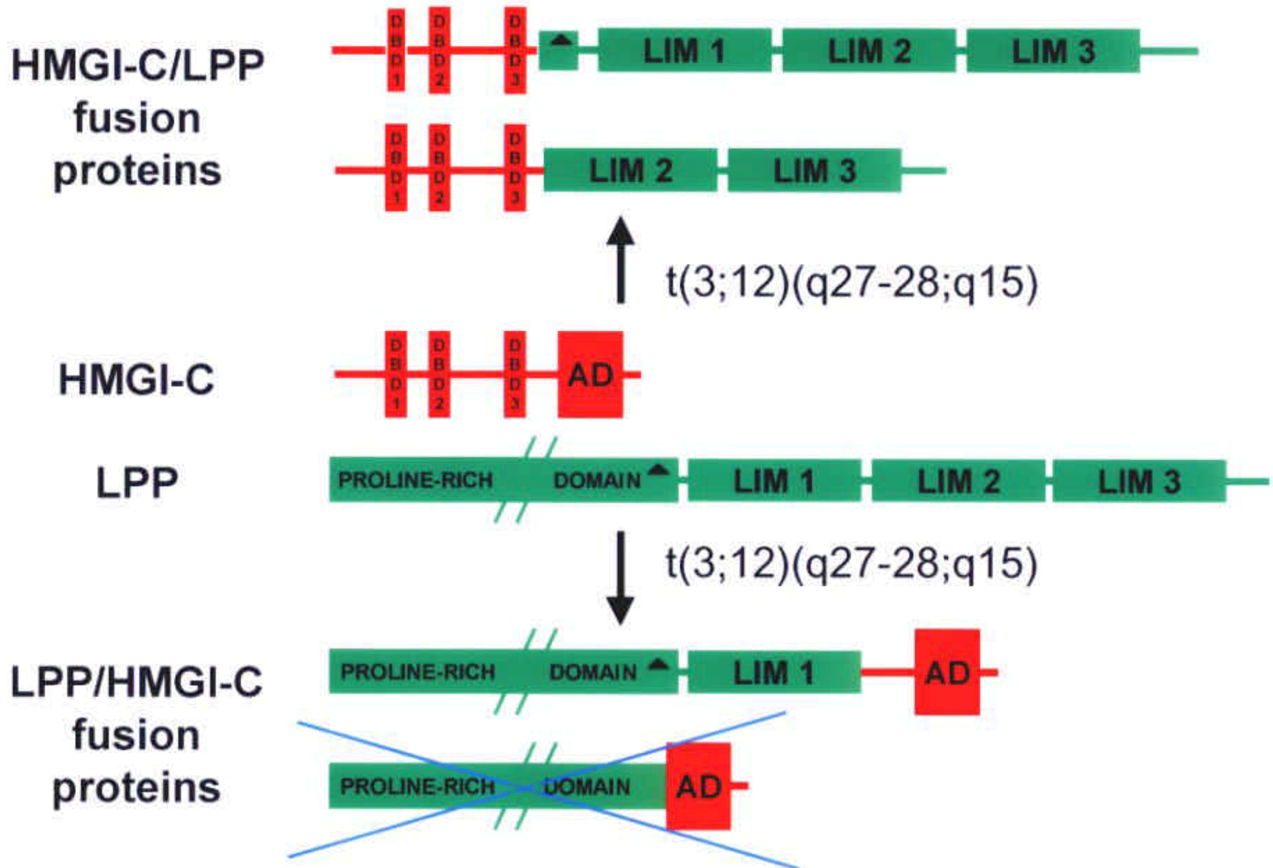

Figure 5. Schematic representation of the HMGI-C/LPP fusion proteins which arise from the chromosome 3;12-translocation. This event is observed in lipomas and pulmonary chondroid hamartomas and affects the proteins encoded by the *HMGI-C* gene on 12q15 and the *LPP* gene on 3q27-28.

sion has been shown to inhibit retrovirally induced transformation resulting in reversal of the transformed phenotype (Berlingieri et al., 1995) and high expression of *HMGI-C* is only observed in early embryogenesis, in cell lines of embryonic origin and in malignantly transformed cells.

The expression of the *HMGI-C* gene itself is under control of various growth-associated factors which were shown to act at the level of transcription initiation (Ayoubi et al., in prep.) and *HMGI-C* is identified as a secondary response gene to oncogenic *Raf-1* activation (Li et al., 1997). The obtained results let us to define *HMGI-C* as a delayed early response gene passing proliferation/differentiation control signals to responsive target genes (**Figure 6**).

V. Concluding remarks and future prospects

The experimental data mentioned in this review, clearly point towards an essential function of HMGI-C in the control of cell growth and proliferation. *HMGI-C* behaves like an oncogene and is therefore potentially a target for therapeutic treatment of tumors which overexpress the gene. Due to the role of HMGI-C in tumor development

and its deregulation in tumors, it is important to understand how *HMGI-C* expression is regulated and which signal transduction pathways are involved in the growth-associated expression of *HMGI-C*. In addition, the exact mechanism by which the HMGI-C protein itself exerts its regulatory effects is not known so far and, therefore, the identification of target genes and functional characterization of the various tumor-derived chimeric HMGI-C fusion proteins may provide insight in the molecular mechanism of solid tumor formation and may be instrumental in the development of potential therapeutic agents interfering with tumor formation.

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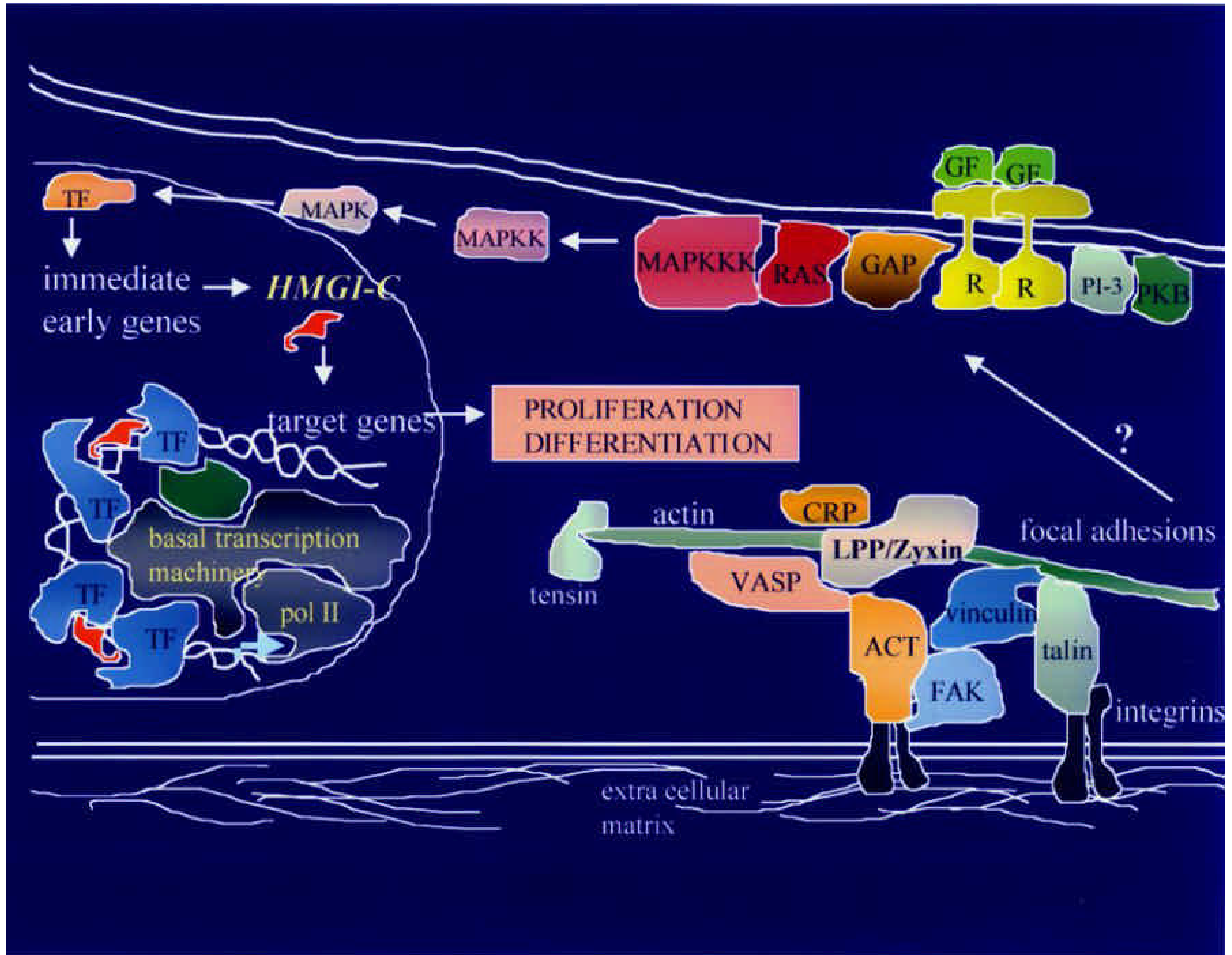

Figure 6. Signal transduction model in which the potential activities of HMGI-C and LPP in the regulation of proliferation and differentiation are indicated.

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