Citation: Cellular Therapy and Transplantation, Vol. 1, No. 1, 23 May 2008, p. 57-60, doi: 10.3205/ctt2008-05-23-001-en

Submitted: 4 February 2008, accepted: 20 March 2008, published: 23 May 2008

Hepatocyte growth factor (HGF) in the pathogenesis of multiple myeloma

By Magne Børset[1,2], Therese Standal[1], Anders Waage[1,3] and Anders Sundan[1]

[1]Department of Cancer Research and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway;
[2]Department of Immunology and Transfusion medicine, St. Olavs University Hospital, Trondheim, Norway;
[3]Department of Hematology, St. Olavs University Hospital, Trondheim, Norway.
Corresponding author: Magne Børset, Norwegian University of Science and Technology, Faculty of Medicine, Department of Cancer Research and Molecular Medicine, Medical Technical Research Center, N-7489 Trondheim, Norway; Telephone: + 47 72573038, Fax: + 47 73598801, E-mail: magne.borset@ntnu.no

Abstract

HGF is emerging as a cytokine with an important role in the pathophysiology of multiple myeloma. Originally identified and described as a growth factor for hepatocytes, HGF was later found to have mitogenic, motogenic, or morphogenic effects on several cell types through its interaction with the tyrosine kinase receptor c-Met. This cytokine–receptor pair is implicated in the development and promotion of several types of cancer. The expression of both HGF and c-Met by myeloma cells is one of the traits distinguishing these cells from healthy plasma cells, and seems to be an early step in tumor development. HGF and c-Met have an effect on proliferation, migration, and adhesion of myeloma cells; and research suggests that myeloma cell-produced HGF is an important factor in angiogenesis and bone destruction seen in the majority of patients with multiple myeloma.

Keywords: multiple myeloma, hepatocyte growth factor, HGF, c-Met, cancer, hematological cancer, DKK1, RANK, RANKL, OPG, carcinogenesis, pathogenesis, bone resorption, bone formation, review

Multiple myeloma (MM)

MM is malignant growth of plasma cells, which are terminally differentiated B lymphocytes[17]. The disease is characterized by production of monoclonal immunoglobulin, by anemia, and by destruction of bone. The malignant myeloma cells are usually located in the bone marrow (BM).

Despite some advances in treatment in recent years, MM still is a persistently fatal disease with a median patient survival time of three to four years from the time of diagnosis. In addition to the dismal prognosis, patients also experience substantial morbidity during the course of the disease. MM therefore continues to be a serious health problem. Standard front-line therapy for patients with MM includes the chemotherapeutic agents melphalan and prednisone, drugs that have been used for this purpose for more than 40 years. Recently, immunomodulatory drugs with putative effect against formation of new blood vessels (e.g., thalidomide), as well as botezomib, a member of an entirely new class of drugs: so-called protesome inhibitors, have shown effects in subsets of patients with MM[18]. However, there is an urgent need for better therapy that is targeted at the weak points of MM.

Our understanding of the molecular etiology of MM has increased enormously over the past ten years[5;19]. Approximately 50% of patients have translocations affecting the immunoglobulin heavy chain locus on chromosome 14. The translocation partner varies, but close to the breakpoint in the partner chromosome, there is a (putative) oncogene that is placed under transcriptional control of an enhancer normally controlling the immunoglobuline heavy chain gene. The ch14 translocations are believed to be early events in the development of MM, and are also present with roughly the same frequency in the premalignant condition "monoclonal gammopathy of undetermined significance"(MGUS) as in overt MM. (There is only a one percent chance per year of progressing from MGUS to MM, so the majority of MGUS cases never develop into MM.) The other 50% of MM cases do not have ch14 translocations, and the early and crucial genetic aberrations in this group of patients are still unknown, but overall, these cases tend to have hyperdiploidy with trisomy of a several recurrent chromosomes. A common theme in all patients with MM is the expression of various isoforms of the cell cycle regulatory protein cyclin-D[5].

Myeloma cells usually do not grow for longer periods in vitro, despite addition of rich growth medium and growth factors. It is generally believed that the cells are dependent on currently unknown factors in the microenvironment of the bone marrow for growth and for protection against apoptosis. At the same time the malignant cells exert a profound influence on the same microenvironment. In overt myeloma there is increased bone marrow angiogenesis[40] and—in most cases—perturbed bone homeostasis[2;3]. It has been known for more than three decades that myeloma cells stimulate osteoclasts, the bone-resorbing cells[28]. A simultaneous reduction in bone formation, leading to an unbalanced bone metabolism

with ensuing erosion of bone substance[4] was also observed many years ago. Factors produced by myeloma cells and either secreted or presented on the cell surface, are believed to be responsible for the perturbed microenvironment, and many candidate factors have been proposed as being responsible for increased bone resorption, with variable experimental documentation.

Role of HGF in the pathogenesis of MM: a mediator of autocrine loops

In 1996 we showed for the first time that myeloma cells express the receptor for HGF, c-Met, and at the same time often produce the ligand HGF[7]. This simultaneous expression of a cytokine and its receptor in the same cell was suggestive of an autocrine stimulatory loop, and we were able to demonstrate that c-Met was indeed activated in the myeloma cell line JJN-3 in an autocrine fashion[8]. Autocrine HGF-driven growth loops have also been demonstrated in other MM cell lines[25]. Later we showed that high levels of HGF in the serum of a patient with MM at the time of diagnosis was an adverse prognostic sign, a finding that has been confirmed by others[26;32]. Recently, we and others have demonstrated that HGF stimulates growth and survival of myeloma cells, and that HGF uses the myeloma marker protein syndecan-1 (CD138) as a co-receptor[13;31]. It has also been shown that myeloma cells express HGF activator, an enzyme converting pre-HGF into the active form of the growth factor[39]. Pre-HGF can also be converted to HGF by urokinase plasminogen activator (uPA)[29]. This enzyme is also produced by MM cells[20]. HGF could also be involved in the migration of myeloma cells to the bone marrow[41]. HGF is important in promoting adherence of MM cells to fibronectin, a matrix protein in the bone marrow environment[23]. Such adhesion is beneficial to the MM cells in the sense that it increases cell proliferation. HGF is also a potent angiogenic factor, and there is a positive correlation between HGF levels in serum and bone marrow angiogenesis in patients with MM, suggesting HGF's role in the excessive angiogenesis seen in these patients[1]. In an abstract presented to the 2006 ASH meeting, D. Hose and colleagues presented data showing that among 89 proangiogic genes only HGF was significantly overexpressed in MM cells compared to normal bone marrow plasma cells[24].

HGF expression is characteristic of malignant plasma cells and distinguishes MM from other closely related diseases

The first comprehensive gene array study of MM by Zhan et al., comparing gene expression in MM cells with that in normal plasma cells, showed that HGF was the only secreted growth factor on the list of the 70 genes that were the most up-regulated of more than 5000 examined genes[44]. Interestingly, HGF was not only expressed in overt MM, but also in BM plasma cells from a majority of patients with MGUS, indicating that initiation of HGF expression is an early event in the transformation of healthy cells into malignant MM cells (Erming Tian and John D. Shaughnessy Jr., personal communication). A recently published gene array study by Chng et al. showed that expression of HGF together with IL-6, a potent growth factor for MM cells, was characteristic for a subgroup of patients with hyperdiploid MM[10]. In another study, using comparative genomic hybridization (aCGH) analysis, recurrent gene copy number alterations were identified, and 47 areas of recurrent gene amplifications were found[9]. HGF was located within a small recurrent amplification that included a total of four genes, and HGF was found to be the only one of those genes with an oncogene-like expression pattern. This amplification was present in more than 40% of patients, and the finding indicates that gene aberrations leading to HGF expression are part of the oncogenic development leading to MM.

In order to identify the gene expression that is important for the specific clinical manifestations of MM, a logical approach would be to compare the gene expression profile of MM cells with that of cells from closely related diseases. This was done with gene array analysis of purified malignant cells from patients with chronic lymphocytic leukemia, Waldenstom macroglobulinemia and MM.[11] Again, HGF stood out as one of the genes that characterized MM as opposed to the two other diseases. Interestingly, the HGF receptor c-Met was also on this list of MM-related genes.

Disturbance of key regulators of bone homeostasis in patients with MM

Skeletal tissue in healthy people is constantly undergoing a balanced remodeling process, where osteoclasts resorb bone and are followed by osteoblasts forming bone. Central to this regulation are specific factors that act directly on osteoclasts and are downstream mediators for many of the systemic bone-active factors. It has become clear that osteoblasts play a crucial role in the direct regulation of osteoclast activity. Osteoblasts express the cell surface protein RANKL, which is necessary for osteoclast differentiation[43]. Furthermore, the osteoblasts express a soluble decoy receptor for RANKL, osteoprotegerin (OPG)[35]. The balance between the two osteoblast products, RANKL and OPG, seems to be critical for the regulation of bone homeostasis.

We have found that multiple myeloma patients have reduced levels of soluble OPG in bone marrow plasma compared to healthy controls[33] and others have found that there is also an increased expression of RANKL in the MM bone marrow[30]. OPG contains a heparin binding site and may bind to heparan sulfates on cells in the bone marrow. We have shown that MM cells bind OPG, presumably via the heparan sulfate-containing protein Syndecan-1[6]. Moreover, we found that this binding led to internalization and degradation of OPG by the myeloma cells[37], thereby providing one possible explanation for the reduced OPG levels in the bone marrow of multiple myeloma patients.

Inhibition of bone formation is important for skeletal destruction in patients with MM

In patients with MM, the balanced process of bone remodeling is upset, leading to degradation of bone and to skeletal morbidity. Intensive research has been conducted to try to unravel the mechanism causing this bone disease. For several decades, the research focus was on factors leading to untimely activation of osteoclasts, although it had long been realized that perturbation in osteoblast function might be equally important[4]. In a mouse model of MM with severe bone disease, osteoblasts were virtually non-existent[22]. Lately, the focus has moved from osteoclasts to osteoblasts, and several papers have contributed to our understanding of osteoblast inhibition[34;38]. Searching for a correlation between gene expression in purified primary MM cells and level of bone disease in the patients, Tian and colleagues identified DKK1, an inhibitor of Wnt signaling, as a prime suspect for the destruction of bone in MM patients[38]. They found that DKK1 inhibited the differentiation of osteoblast precursors into mature bone-forming osteoblasts. Later studies seem to confirm that DKK1 is linked to excessive bone disease and that it works by inhibiting the formation of osteoblasts[16;42]. Interestingly, genes that encode known osteoclast-regulating factors, such as RANKL,

RANK, OPG, MIP1, PTHrP, and IL-1, did not show a significant relation to the presence of bone disease[27]. This is not a proof against these factors as important for bone destruction in MM, but argues against MM cells as the source of them. Similarly, osteoclast-activating factors were conspicuously absent from the list of gene expression that was characteristic for MM cells; as opposed to cells from chronic lymphocytic leukemia and Waldenstom macroglobulinemia[11]. Bone disease is not a common clinical trait of the latter two diseases, and one would expect the genes that are responsible for this hallmark of MM to be present on the list of genes that define the specific cancer phenotype of MM. Like HGF and c-Met, DKK1 was high up on this list, further supporting the role of DKK1 in promoting the bone disease that is linked to MM.

HGF inhibits bone morphogenetic protein-induced differentiation of mesenchymal stem cells into bone-forming osteoblasts

Since HGF is one of the genes distinguishing malignant plasma cells from healthy plasma cells, and also defines malignant plasma cells as opposed to other closely related malignant cells, it was logical to see whether HGF played a role in bone homeostasis. It had been previously published that HGF induces bone resorption by osteoclasts, but only in the presence of osteoblasts[15]. This indirect effect on osteoclasts could be partly through HGF-induced production of IL-11, an osteoclast-stimulating cytokine[21]. Bone morphogenetic proteins (BMP) promote differentiation of osteoblast precursors from mesenchymal stem cells (MSCs) and further maturation into bone forming osteoblasts. Experiments by our group showed that HGF inhibited BMP-induced expression of alkaline phosphatase in human MSCs and in the murine myoid cell line C2C12[36]. HGF also prevented BMP-induced mineralization by human MSCs. Furthermore, the expression of the osteoblast-specific transcription factors Runx2 and Osterix was reduced by HGF treatment. Interestingly, HGF promoted proliferation of human MSCs, whereas BMP halted the proliferation. Again, HGF was a key regulator, keeping the cells in a proliferative, undifferentiating state despite the presence of BMP. BMP-induced nuclear translocation of receptor-activated Smads was inhibited by HGF, providing a possible explanation as to how HGF inhibits BMP signaling. These findings support a role of HGF similar to that of DKK1. By preventing MSCs from becoming mature osteoblasts, the osteoblast precursors are arrested in an intermediate stage of differentiation, where they express RANKL, an osteoclast-stimulating protein. Therefore, instead of contributing to bone repair, these cells promote the bone-destruction process: bone homeostasis is no longer balanced. Was there any clinical evidence that HGF really played this role as an osteoblast inhibitor in patients? Yes, the in vitro data were supported by the observation of a significant negative correlation between HGF and a marker of osteoblast activity, bone-specific alkaline phosphatase, in sera from 34 patients with myeloma[36].

Targeting HGF hepatocyte growth factor and its receptor c-Met in multiple myeloma

Since expression of HGF seems to be an early oncogenic event in the development of MM, and due to HGF's many effects on disease manifestations, it might be an attractive target in treatment of MM. A host of new pharmacological inhibitors of c-Met are in the pipelines of the pharmaceutical industry. Possible HGF inhibitors include small molecular drugs and antibodies, as well as naturally occurring splice variants of HGF with antagonistic or partially antagonistic effects on c-Met. NK4 belongs to the latter group: a variant of HGF that lacks part of the full molecule[12]. This molecule was shown to block growth of MM cell line cells in a mouse model, an effect that was believed to be a combination of direct anti-proliferative effect of the drug on MM cells, as well as an indirect, anti-angiogenic effect on formation of new blood vessels[14]. PHA-665752, a novel pharmacological inhibitor of c-Met from Pfizer belongs to the group of small molecular inhibitors. This molecule prevented HGF-driven autocrine loops in an MM cell line, as well as in freshly isolated MM cells from myeloma patients[25]. No in vivo data on effects on MM cells of small-molecule inhibitors of c-Met have been published yet, and no clinical trial with c-Met inhibitors has been started so far. However, the data from such studies are sure to be met with great anticipation.

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Ссылка: Клеточная терапия и трансплантация, том 1, номер 1, 23 мая 2008, с. 60-61, doi: 10.3205/ctt2008-05-23-001-ru-a

Роль фактора роста гепатоцитов (HGF) в патогенезе множественной миеломы

М.Борсет, Т.Стандал, А.Вооге, А.Сундан

Расширенное резюме

Множественная миелома (ММ) - это плазмоклеточная злокачественная опухоль с поражением костного мозга, которая сопровождается продукцией моноклонального иммуноглобулина, анемией и деструкцией кости. Неизлечима. Генетическая основа ММ гетерогенна: в приблизительно половине наблюдений ММ имеются транслокации с участием, с одной стороны, хромосомы 14 (ген IgH), и с другой – ряда хромосом с точкой разрыва

вблизи локализации различных онкогенов. Эти мутации относятся к раннему онкогенезу. В остальных случаях наблюдается гипердиплоидия с трисомиями нечетных хромосом. Вне зависимости от характера генетического дефекта в опухолевых клетках обнаруживается гиперэкспрессия циклинов D. Миеломные клетки (МК), как правило, не растут в искусственных средах; это позволяет считать, что они критически зависимы от ряда еще не известных факторов, которые содержатся в костном мозге. МК стимулируют рост сосудов и функцию остеокластов.

HGF является фактором аутокринной стимуляции МК. Экспрессия HGF характерна для МК и отличает ММ от родственных опухолей. МК часто коэкспрессируют HGF и его рецептор c-Met и могут секретировать вещества, переводящие HGF в активную форму, в т.ч. активатор плазминогена. Маркер плазматических клеток CD138 (синдекан-1) является корецептором HGF. HGF стимулирует миграцию и адгезию МК и таким образом может иметь значение в удержании МК в костном мозге. Кроме того, HGF, по видимому, стимулирует ангиогенез. Ген HGF является единственным из 70 генов факторов роста, и единственным из генов, кодирующих проангиогенные белки, гиперэкспрессированным в МК, по сравнению с нормальными плазматическими клетками. Гиперэкспрессия гена HGF была обнаружена и у части больных с MGUS (моноклональная гаммапатия неясного значения), указывая на вероятную роль HGF на ранних этапах опухолевого роста. Показано, что ген HGF включен в состав короткого фрагмента из 4 генов, который амплифицирован у значительной части больных ММ. При этом гиперэкспрессия HGF не обнаруживается у больных хроническим лимфолейкозом (ХЛЛ) и макроглобулинемией Вальденстрема. Высокие уровни HGF в сыворотке больных ММ ассоциированы с неблагоприятным прогнозом.

Нарушения регуляции гомеостаза кости у больных ММ. Подавление остеогенеза не менее важно, чем стимуляция резорбции. Деструкция кости - одно из важнейших проявлений ММ. Гомеостаз кости во многом определяется балансом двух белковых продуктов остеобластов – RANKL (необходим для созревания остеокластов) и остеопротегерина (растворимый рецептор-ловушка для RANKL). При ММ концентрация растворимого OPG в костном мозге ниже, а концентрация RANKL – выше, чем у здоровых. МК способны связывать OPG, по видимому, с помощью синдекана-1, с последующей интернализацией и деградацией.

До настоящего времени не обнаружено связи между степенью выраженности костного синдрома и активацией генов важнейших факторов, стимулирующих остеокласты (RANKL, RANK, OPG, MIP1, PTHrP, и IL1), а также различий экспрессии этих генов при ММ, ХЛЛ и макроглобулинемии Вальденстрема. В то же время показано, что экспрессия DKK-1 (ингибитор Wnt-зависимого сигналинга, ингибирует дифференцировку предшественников остеобластов) при ММ пропорциональна тяжести костной патологии.

HGF ингибирует дифференцировку мезенхимальных стволовых клеток в остеобласты, индуцированную морфогенетическими протеинами кости (BMP). HGF стимулирует резорбцию кости остеокластами, но только в присутствии остеобластов. Частично этот эффект может объясняться продукцией IL-11 остеобластами под действием HGF. Основным индуктором остеобластической дифференцировки мезенхимальных стволовых клеток являются морфогенетические белки кости (BMP). HGF стимулирует пролиферацию и тормозит дифференцировку мезенхимальных стволовых клеток, несмотря на присутствие BMP. В результате недостаточно дифференцированные остеобласты еще не способны к синтезу кости, но уже экспрессируют на своей поверхности RANKL – белок, стимулирующий остеокласты. В пользу существования такого механизма говорит и сильная отрицательная связь между концентрацией HGF и остеоспецифической щелочной фосфатазы (маркер активности остеобластов) в сыворотке крови больных ММ.

HGF и c-Met как потенциальные мишени терапии. Учитывая многогранность эффектов HGF в отношении миеломных клеток и их микроокружения, рассматривается возможность использования антагонистов HGF/c-Met в качестве лекарственных средств. Ингибиторы HGF/c-Met включают низкомолекулярные ингибиторы, антитела и естественные сплайс-варианты HGF с полным или частичным антагонизмом. К последним относится NK4, представляющий собой часть молекулы HGF. NK4 блокирует рост миеломных клеточных линий в мышиной модели, вероятно, путем прямого торможения пролиферации МК и опосредованного торможения роста сосудов. К группе низкомолекулярных ингибиторов c-Met относится PHA-665752 (Pfizer). В наших экспериментах PHA-665752 подавлял стимуляцию c-Met и ее последствия как в клеточных линиях, так и в клетках пациентов с ММ. Результаты возможного клинического применения ингибиторов HGF/c-Met представляют несомненный интерес.

Ключевые слова: Миеломная болезнь, онкогематология, фактор роста гепатоцитов, c-Met, RANK, RANKL, остеопротегерин (ОПГ), канцерогенез, костная резорбция, остеогенез, обзор