group of related proteins that not only induce formation of cartilage and bone but now are also regarded as multifunctional cytokines.[3] BMP-2, as 1 representative of the 20 hitherto described BMPs, also plays a key role in osteoblast differentiation and induces apoptosis in myeloma cell lines and in primary samples from patients with myeloma.[4]

The definite origin of BMP-2 production in myeloma is uncertain, although it is likely to derive directly from bony tissue such as chondrocytes[4] and possibly from bone marrow stroma cells. Increased BMP-2 production may reflect a counterbalance to excessive bone degradation and a defense mechanism against the proliferating myeloma cells by down-regulation of Bcl-xL, by cell-cycle arrest through up-regulation of the cyclin kinase inhibitors p21 and p27, and by hypophosphorylation of the retinoblastoma protein. Furthermore, BMP-2 has been shown to result in immediate inactivation of STAT3 leading to the disruption of the IL–6 –signaling pathway.[5]

In myeloma, increased hepcidin levels have been reported by several investigators.[2,6] Hepcidin plays an important role in inflammation by restricting intestinal iron absorption and macrophage iron release. Its expression is modulated in response to body iron stores, hypoxia, and infectious and inflammatory stimuli. Among the inflammatory cytokines, IL-6 is an effective inducer of hepcidin but according to the results of Maes et al, BMP-2 seems to be an even more important hepcidin stimulator in patients with myeloma. Increased hepcidin levels result in iron-restricted normochromic anemia characterized by hypoferremia, normal to increased ferritin, and reduced transferrin saturation.[7] Body iron stores usually are normal or increased, but due to the described alterations the available iron cannot be used by the erythropoietic marrow. This so-called anemia of chronic inflammation is probably the most frequent cause of anemia in multiple myeloma. Other frequent causes or contributory factors of anemia in myeloma are decreased erythropoietin production as a consequence of clinical apparent or subclinical renal impairment, reduced sensitivity of erythroid precursors to erythropoietic stimuli, suppression of erythropoiesis by antimyeloma therapy, dilutional anemia due to hypervolemia, and, in some cases, direct myeloma cell–mediated apoptosis of erythropoietic precursors.[8] Overall, approximately 50% to 60% of patients present with overt anemia at diagnosis and up to 90% develop anemia during myeloma therapy.

As the available treatment options for chronic anemia of myeloma—such as red cell transfusions, erythropoietic agents, or intravenous iron supplementation—are less than optimal, the question arises of whether the results of this study can be exploited for the design of new treatment concepts. Inhibition of BMP-2 should reduce hepcidin production but is unlikely to result in complete abrogation of hepcidin stimulation because of the increased production of various cytokines with hepcidin–inducing activity. In addition, inhibiting BMP-2 may be counterproductive, given its important role in osteoblast, cartilage, and bone formation and possibly, even more importantly, its antimyeloma activity. Subject to these considerations, hepcidin seems to be the logical target for therapeutic intervention, because high hepcidin expression is sufficient to cause anemia and resistance to endogenous erythropoietin.[9] In fact, hepcidin depletion by neutralizing antibodies or by hepcidin small-interfering RNAs was shown to restore normal hemoglobin levels in a mouse model of anemia of chronic inflammation when applied in combination with erythropoietic agents.[10] Other approaches to hepcidin inhibition are inhibitors of the stimulatory pathways for hepcidin transcription or strategies that block the effect of hepcidin on its only known cellular target ferroportin. Progress in this area could revolutionize treatment of anemia of chronic inflammation and, hence, treatment of the most common cause of anemia in myeloma.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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● ● ● **TRANSFUSION MEDICINE**

Comment on Chen et al, page 3660

FNAIT: the fetus pleads guilty!

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Fetal/neonatal alloimmune thrombocytopenia (FNAIT) resulting from fetal platelet destruction by maternal alloantibodies is the most common cause of severe fetal thrombocytopenia and of neonatal thrombocytopenia in maternity wards.[1] The pathophysiology is largely unknown. The fetus has long been considered as an "innocent bystander."

In this issue of *Blood*, Chen and colleagues, using murine models, demonstrate that the fetal, not maternal, major histocompatibility complex class I–related neonatal Fc receptor (FcRn) is implicated in the transplacental transfer of maternal antibodies and show that monoclonal antibody specific to FcRn may be effective in this disease.[2]

FNAIT (1/1000 live births) is usually discovered incidentally.[3] The complication most feared is intracranial hemorrhage, leading to death or neurologic sequelae.[4] If the fetus in a subsequent pregnancy is also platelet antigen incompatible, the condition is usually more severe, so antenatal management has been proposed with weekly maternal administration of intravenous immunoglobulins (IVIG).[5] This treatment is relatively effective. However, this therapy relies on a human-derived product; it is expensive and in some cases
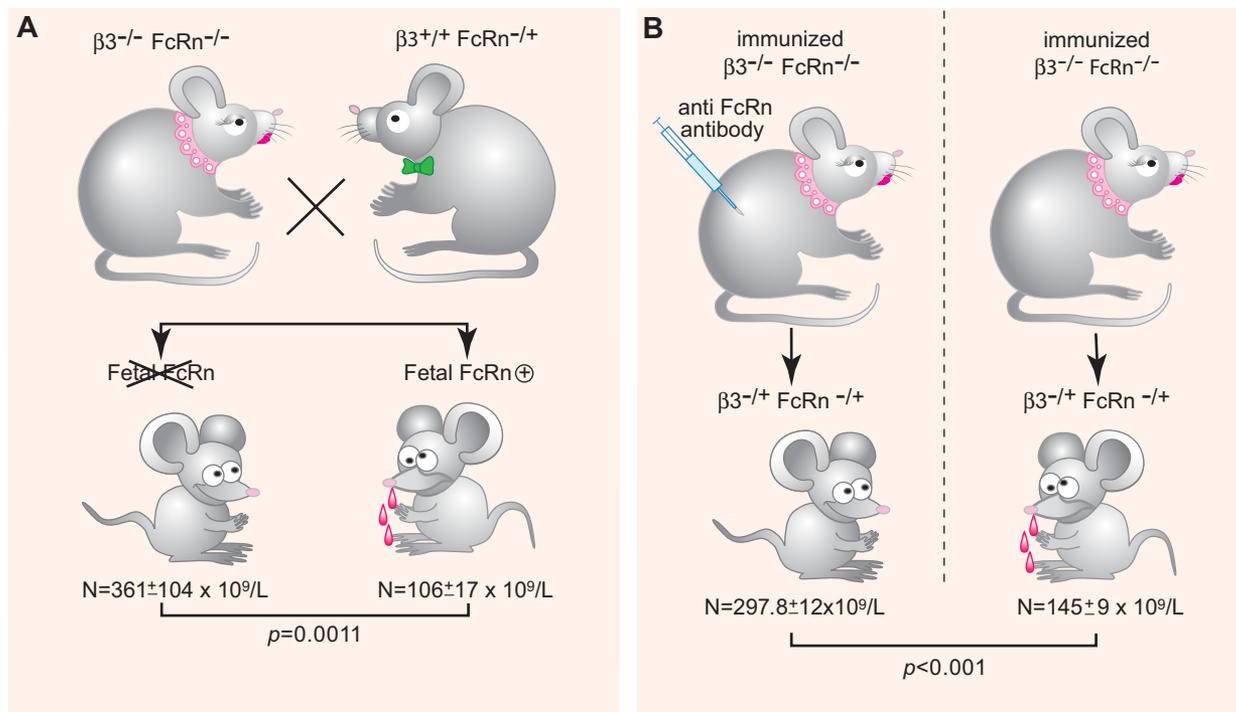
FcRn a key factor in FNIT. (A) Fetal FcRn is required for FNIT. Low platelet counts are observed only in pups expressing fetal FcRn delivered from immunized β3$^{-/-}$FcRn$^{-/-}$ × β3$^{+/+}$FcRn$^{-/+}$. (B) Anti-FcRn monoclonal antibody injection during pregnancy. Low platelet counts are observed only in pups delivered from nontreated immunized female mice. N = platelet counts. (Professional illustration by Paulette Dennis.)

therapy failures have been observed. Other approaches are therefore under study.[6]

Chen et al focus on the FcRn receptor, its role in the pathophysiology of fetal/neonatal immune thrombocytopenia (FNIT) and as a possible target for therapy. In fetal medicine, direct human research is usually not possible for ethical reasons. To address these questions the authors have developed several knockout murine models[7] and monoclonal antibodies. The model they established is more similar to human platelet isoimmunization (the recipient lacks glycoprotein) than alloimmunization (immunization resulting from single amino-acid substitution); however, the major clinical effect of interest, that is, thrombocytopenia, is present in pups.

FcRn was characterized in the 1980s. This receptor is involved in the specific transport of IgG from the mother to the fetus. In rodents, FcRn is expressed on the cell-surface brush border of enterocytes. It has been shown that FcRn functions most efficiently in the neonatal period when pups ingest maternal milk containing IgG.[8] In humans, the maternal IgG transfer occurs antenatally via the placenta.

To identify more accurately the mechanisms responsible for mediating the transport of IgG maternal antibodies, Chen et al established a new model of FNIT using combined β3/FcRn–deficient mice. They document that anti-β3 integrin antibodies could be generated and maintained at a relatively high level in double β3/FcRn knockout mice immunized with β3 platelets. They demonstrate that FcRn is essential in the cross-placental passage of maternal antibodies by showing β3$^{-/+}$FcRn$^{+/+}$ pups having lower platelet counts than heterozygous β3 pups lacking FcRn. Chen and colleagues also reviewed the respective roles of maternal and fetal FcRn, clearly showing that fetal FcRn was the predominant effector for transplacental IgG transport and the resulting induction of low platelet counts in pups (see figure, panel A); in addition, they investigated whether FcRn may be a therapeutic target in FNIT.

Throughout life, FcRn plays a critical role in regulating the levels and persistence of IgG. Modulating the interaction of IgG with FcRn allows development of a new therapy in antibody-mediated diseases.[9] To address this specific issue, Chen et al produced a new anti-FcRn monoclonal antibody. They found that pups delivered from anti-β3–immunized female mice treated with this antibody have higher platelet counts than those delivered from nontreated immunized mice (see figure, panel B), suggesting that such an antibody may be considered as a therapeutic agent.

The last part of the study examines the potential role of FcRn in the mechanisms involved in the action of IVIG.[10] Reports favor saturation of FcRn, leading to increased catabolism of pathogenic antibodies.

Chen et al show that IVIG is able to down-regulate anti-β3 antibodies in immunized female mice—also in the absence of FcRn—and to increase platelet counts in pups delivered from IVIG-treated mice. This article makes new contributions, establishing that fetal FcRn is a key factor in the transplacental passage of maternal antibodies and may be considered as a potential therapeutic target. However, translating these results from murine models to humans should be done with caution; open questions remain. The placental structure varies remarkably across species. Humans and mice express different Fc receptors and FcRn-IgG interactions may differ between species. Animal models expressing human receptors and in vitro studies using human placental lobules are to be considered.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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● ● ● ● **VASCULAR BIOLOGY**

Comment on Mitola et al, page 3677

Gremlin: vexing VEGF receptor agonist

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Gremlins are mischievous creatures in English folklore, believed to be the cause of otherwise unexplainable breakdowns (the word gremlins is derived from the Old English "gremian" or "gremman," "to vex"). Gremlin (or Gremlin-1) is also the designation of a secreted protein that is known to regulate bone formation during development. In this issue of *Blood*, Mitola et al report the novel role of Gremlin as a VEGFR2 agonist[1] and the function of the Gremlin protein seems vexing indeed.

Schematic outline of Gremlin's dual role in tumor biology. Neutralization of BMPs may result in attenuation of suppressive signaling, whereas stimulation of VEGFR2 promotes angiogenesis. (Professional illustration by Marie Dauenheimer.)

Gremlin was originally identified as a member of a *Xenopus laevis* protein family regulating broad processes in growth and development; independently, Gremlin was identified as a rat variant denoted "Drm" (down-regulated in mos-transformed cells).[2] The secreted Gremlin proteins have been shown to exert their effects by blocking the function of specific bone morphogenetic proteins (BMPs),[2] which belong to the transforming growth factor β (TGFβ) superfamily. Gremlin binds to and inhibits the function of BMP2, BMP4, and BMP7, which in turn regulate limb development. In accordance, inactivation of the *grem1* gene in mice causes skeletal malformation and increased bone formation whereas overexpression causes inhibition of bone formation and osteopenia.[2] Thus, whereas Gremlin plays an important role in bone development, its function, if any, in adult physiology is unknown.

Mitola et al now show that Gremlin binds with high affinity to the important vascular endothelial growth factor (VEGF) receptor in endothelial cells, VEGF receptor-2 (VEGFR2). Biochemically, Gremlin behaves surprisingly similar to VEGF in its activation of VEGFR2; it induces tyrosine phosphorylation of the receptor, as well as downstream signaling, resulting in endothelial cell proliferation, migration, and formation of angiogenic sprouts.[3]

From a structural point of view, it is not entirely surprising that Gremlin would bind to VEGFR2. Gremlin and VEGF (as well as TGFβ and platelet-derived growth factor [PDGF]) all share a structural cysteine-knot motif.[2,4] The concept that one receptor molecule can bind structurally distinct ligands is also not new. Mitola et al[1] show convincingly that Gremlin indeed is a potent and specific VEGFR2 agonist which competes out binding of VEGF in a dose-dependent manner.

However, it is unclear at this point to what extent VEGF and Gremlin overlap biologically. Whereas VEGF/VEGFR2 is tightly linked to angiogenesis, both in physiology and pathology such as in the growth of cancer,[3] the biology of Gremlin/VEGFR2 is not obvious and in vivo studies remain to be performed. There is as yet no data that ties Gremlin directly to tumor angiogenesis. Of note, Gremlin is expressed in a range of human cancers (carcinomas of the uterine cervix, lung, ovary, kidney, breast, colon, and pancreas, see Sneddon et al[5]), where it has been suggested to
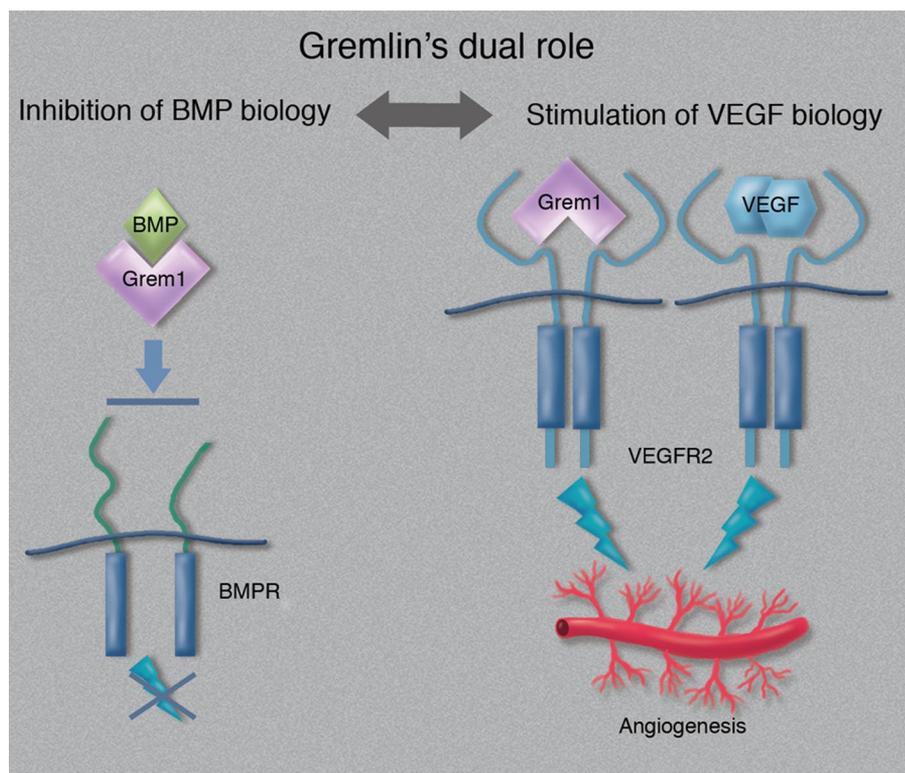
FNAIT: the fetus pleads guilty!

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