outcome, the figure shows these findings as a schematic diagram.

Given the novel asparaginase-dexamethasone pharmacokinetic interaction described by Kawedia et al, there are several simple strategies that may minimize allergic reactions to asparaginase and have the double benefit of improved effectiveness of both asparaginase and dexamethasone therapy. Pretreatment with glucocorticoids is expected to decrease the likelihood of development of anti-asparaginase antibodies. Regimens that use a "continuous" asparaginase dosing schedule (eg, weekly *Escherichia coli* at 25 000 IU/M2) rather than "pulse" dosing (eg, *E coli* 10 000 IU/M2 3 doses/wk for 6 doses/course repeated over 6 weeks apart) are less immunogenic.[7] Change to an alternate asparaginase preparation (eg, *E coli* or pegaspargase to *Erwinia*) is beneficial especially if done early with any suggestion of allergy either by clinical symptoms, measurement of asparaginase antibody, enzyme activity level, or a surrogate marker of asparaginase effect such as albumin.[7-10] Development of a simple, inexpensive assay for anti-asparaginase antibody or asparaginase enzyme activity that could be readily accessible to clinicians would allow prospective modifications of both asparaginase and dexamethasone dosages to optimize exposure for both drugs in a single patient. Such assays would be particularly useful to identify patients who are at risk for diminished asparaginase effect as well as increased dexamethasone clearance and decreased dexamethasone exposure because of "silent hypersensitivity." The phrase "silent hypersensitivity" is used to describe the phenomena of development of anti-asparaginase antibodies and frequently increased clearance rate of asparaginase without overt signs of allergic reaction.[7] These approaches, however, have not been evaluated in a prospective trial.

Dexamethasone and asparaginase together during induction therapy have proven very effective. Because of significant toxicities, however, the use of this combination has been limited to our youngest and lower-risk patients. In fact, our higher-risk patients including adolescents and young adults as well as patients with T-cell disease stand to benefit the most from this combination as long as the risks could be minimized. The data suggest that re-examination of induction regimens that use asparaginase and dexamethasone is warranted to test if optimal asparaginase effect (because asparaginase antibody formation is rare during induction) would allow a lower dexamethasone dose to be used. The lower dose of dexamethasone would be feasible if it provided systemic exposure that was efficacious yet not toxic in terms of increased risk of infection and severe osteonecrosis. As shown in the figure, there are additional factors such as age and concomitant treatment with certain drugs that also influence drug exposure to dexamethasone. The major challenge will be in defining the optimal dexamethasone exposure that balances efficacy and toxicity within the context of concurrent asparaginase therapy for all age groups, risk categories, and immunophenotypes.

Despite the numerous advances in diagnosis, intensive risk-directed therapy, and supportive care measures, some children are not cured. This clinical pharmacologic study underscores the importance of individualized therapy: the right dose for the right patient. One size does not fit all.

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● ● ● HEMATOPOIESIS & STEM CELLS

Comment on Ichii et al, page 1683

Wnt cross-talk in the niche

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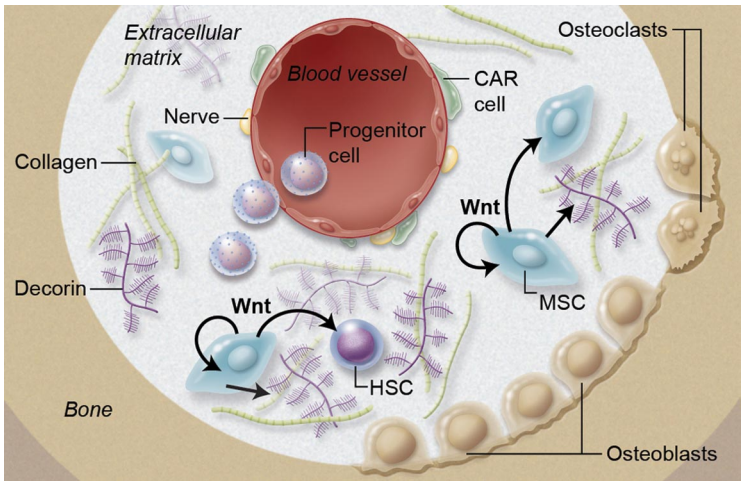
Mesenchymal stromal cells (MSCs) overexpressing the *Wnt3a* gene support hematopoiesis at least in part via Wnt-dependent production of extracellular matrix proteoglycans. Canonical Wnt signaling is known to have direct effects on hematopoietic stem cell (HSC) function.

In this issue of *Blood*, Ichii et al demonstrate that Wnt signaling also affects stromal components, thereby regulating the architecture of the hematopoietic niche.[1] They demonstrate that human HSCs are retained, while B-cell development is inhibited and lineage-committed progenitors can dedifferentiate when exposed to MSC lines that express the canonical Wnt gene *Wnt3a*.[1] The opposite occurred when the noncanonical *Wnt5a* gene was used.

Wnt signaling is required for several basic developmental processes. Wnt signaling plays a crucial role during hematopoiesis and development of myeloid and T lymphoid cells (reviewed in Staal et al[2]). There are at least three different Wnt pathways: the canonical Wnt pathway, which involves β-catenin and members of the T-cell factor (Tcf)/lymphocyte-enhancer binding factor (Lef) family; the planar cell polarity (PCP) pathway; and the Wnt-$Ca2^+$ pathway. The latter two pathways



It is well established that Wnt can directly influence HSCs; however Wnt also regulates MSCs, which become more supportive of hematopoiesis. Ichii and coworkers show that this is at least in part mediated by Wnt-dependent production of extracellular matrix component *Decorin*, thereby proving a Wnt-dependent cross-talk between MSCs and HSCs. Professional illustration by A. Y. Chen.

are referred to as noncanonical Wnt pathways. It is generally accepted that canonical Wnt signaling is one of the key factors underlying self-renewal of many types of stem cells, including HSCs. Fetal liver HSCs deficient for Wnt3a lack self-renewal because of a complete loss of canonical Wnt signaling.[3] Likewise, adult HSCs that lack Wnt signaling by overexpressing DKK1, a Wnt sequestering and inhibitory protein, are unable to self-renew.[4]

The role of canonical Wnt signaling in HSCs has been quite controversial because of conflicting results in various gain- and loss-of-function studies. By carefully studying the levels of Wnt signaling in these various models, it has now become clear that Wnt is regulated in a dosage-dependent fashion at key checkpoints in various lineages of the hematopoietic system.[5] HSCs both require and tolerate only relatively low levels of Wnt signaling, compared with developing T cells or other types of stem cells, for instance, those in the intestine.[5] On the other hand, complete absence of Wnt signaling in HSCs severely impairs their repopulating capacity.[3,4]

While most attention has been on direct effects of Wnt proteins on HSCs, the work reported here by Ichii et al shows that Wnt mediates cross-talk of MSCs and HSCs via Wnt-dependent production of *Decorin*, an important extracellular matrix component (see figure).[1] *Decorin* "decorates" collagen and other molecules with proteoglycans, thereby shaping the niche. It should be noted that these findings were generated using MSC lines, not primary MSCs. Yet the incredibly high up-regulation of *Decorin* in MSC lines was followed by studies checking various primary niche cells, again showing high *Decorin* expression in MSCs but not hematopoietic cells or CXCL12 abundant reticular cells. Indeed, *Decorin*-deficient mice where shown to have a complex hematopoietic phenotype, with extramedullar hematopoiesis and increased numbers of $CD150^+$ LSK, the phenotype of LT-HSC in the mouse.

HSC self-renewal, specification and differentiation are complex processes regulated by intricate networks of signals that have to be tightly orchestrated and "fine-tuned" to correctly drive these processes. Recent work by Schaniel and coworkers shows that changes in Wnt signaling in the HSC niche also influence the fine-tuning of other pathways including the hedgehog pathway.[6] This pathway is no less controversial than Wnt in regulating HSCs. Similar to Wnt, it is also involved in leukemia development.[7] Interestingly, in the normal stem cell niche, Wnt signaling restricts self-renewal by providing a local dosage-dependent gradient of Wnt proteins, akin to the function of Wnts in lower vertebrates as true morphogens. In contrast, in the AML niche Wnt can no longer exert this type of regulation as the leukemic stem cells have undergone mutations rendering them independent of extracellular Wnt proteins.[8] It will be of interest to compare the contributions of cell autonomous versus extracellular signals in normal and leukemic stem cell niches for various important self-renewal signals.

The current work also points to the possibility that changes in the microenvironment, including MSCs, can contribute to dysregulated signals leading to leukemia. It has been previously suggested that altered gene expression in osteoprogenitors may induce bone marrow dysfunction with myelodysplasia and subsequently leukemias.[9] Such proleukemic alterations in MSCs are therefore not unprecedented and point to many possibilities of future research on both normal and malignant hematopoiesis. Finally, as Ichii and coworkers demonstrate, the genetic modification of MSCs can alter their functional and differentiation properties dramatically. Because MSCs are used clinically to successfully treat various diseases, including GVHD[10] and provide hematopoietic support, use of genetically altered MSCs offers a potential novel treatment modality.

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