			T cells, mouse*		Splenocytes, rat[3]		DCs, human[4]		Monocytes, human[5]	
Receptor subtype	Signal	Antagonist[1]	R	A	R	A	I	M	R	A
5-HT$_{1A}$	G$_{i/o}$	WAY100635	–	–	–	–	–	–	–	–
5-HT$_{1B}$	G$_{i/o}$	SB236057	+	_§	+	+	+	±	–	–
5-HT$_{1D}$	G$_{i/o}$	BRL15572	–	–	–	–	–	–	–	–
5-HT$_{1E}$	G$_{i/o}$	None	n/a¶	n/a¶	n/a¶	n/a¶	+	±	+	+
5-HT$_{1F}$	G$_{i/o}$	None	–	–	+	+	–	–	–	–
5-HT$_{2A}$	G$_{q/11}$	MDL100907	–	+	+	+	+	+	+	+
5-HT$_{2B}$	G$_{q/11}$	RS127445	–	–	+	+	+	±	–	–
5-HT$_{2C}$	G$_{q/11}$	SB242084	–	–	–	–	–	–	–	–
5-HT$_{3}$	Ion chan.	Ondansetron	–	–	–	+	+	+	+	+
5-HT$_{4}$	G$_{S}$	SB204070	–	–	–	–	±	+	+	+
5-ht$_{5A}$	Multiple?	SB699551A	–	–	–	–	–	–	–	–
5-ht$_{5B}$	Unknown	None	–	–	–	–	n/a#	n/a#	n/a#	n/a#
5-HT$_{6}$	G$_{S}$	SB271046	–	–	–	–	–	–	–	–
5-HT$_{7}$	G$_{S}$	SB656104	+	+	+	+	±	+	+	+

Reported expression of 5-HT receptor transcripts in immune cells. Synthesis of findings from studies by *León-Ponte et al in this issue of *Blood* and from Stefulj et al,[3] Idzko et al,[4] and Durk et al[5] highlighting the repertoire of 5-HT receptor subtype of mRNA expressed in immune cells. R indicates resting; A, activated; I, immature; M, mature; Ion chan., ligand-gated ion channel; −, negative; +, strong signal; and ±, weak signal. §5-HT1B protein increased on activation. ¶Absent from mouse and rat. #Truncated transcript in human. Illustration by Frank Forney.

rodents).[1,2] Using reverse transcription–polymerase chain reaction (RT-PCR), the authors ruled out SERT and all but 3 receptor subtypes: only 5-HT$_{1B}$, 5-HT$_{2A}$, and 5-HT$_{7}$ receptors remaining to deliver the 5-HT hit. While not excluding contributions from 5-HT$_{1B}$ and 5-HT$_{2A}$ receptors, the authors homed in on 5-HT$_{7}$ as the major player: this 7-transmembrane domain G protein–coupled receptor (GPCR) assisted T-cell stimulation by promoting ERK1/2 phosphorylation and canonical NFκB activation. Not only were the authors able to attenuate 5-HT–dependent change with a selective 5-HT$_{7}$ receptor antagonist but, by using a 5-HT$_{7}$ receptor agonist, were able to reverse otherwise defective T-cell stimulation arising as a consequence of having blocked tryptophan hydroxylase (TPH), the rate-limiting enzyme in the conversion of tryptophan to 5-HT. Tryptophan is also the catabolic substrate for indolamine-2,3-dioxygenase (IDO), and the relative abundance/activity of TPH, IDO, and, additionally, metabolizing monoamine oxidases (MAOs) could determine 5-HT output from immune cells.

While the present study marks a significant advance, the authors themselves address seeming inconsistencies between this and isolated reports on the relative importance of individual 5-HT receptor subtypes to T-cell function, and rightly posit additional questions. Issues include strain and species differences, tissue and subset heterogeneity, and methodological concerns.

Few studies have attempted such an extensive survey of an immune cell's 5-HT receptor repertoire as the one here. The table summarizes and compares the study's salient features with 3 others of merit: a pioneering study on rat splenocytes[3] and, from Idzko and colleagues, separate analyses of receptor subtype distribution on human dendritic cells (Idzko et al[4]) and monocytes (Durk et al[5]). Of the discordant and common themes, the near-universal expression of 5-HT$_{7}$ receptors—irrespective of cell type or animal species—is striking. A built-in knowledge of the pharmacology and signaling properties of 5-HT receptors (see table), driven by and gained largely through their contribution to CNS pathways, holds promise for the ready translation of 5-HT receptor therapeutics to immunology and hematology clinics once a more robust integration of their place in immune physiology—and pathology—has been secured.

The authors are directors and cofounders of Celentyx Ltd, a spinout company whose activities include the profiling of serotonergic compounds against immune cells. ■

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NEOPLASIA

Comment on Zhao et al, page 3432

The CBFB-MYH11 butterfly effect in hematopoiesis

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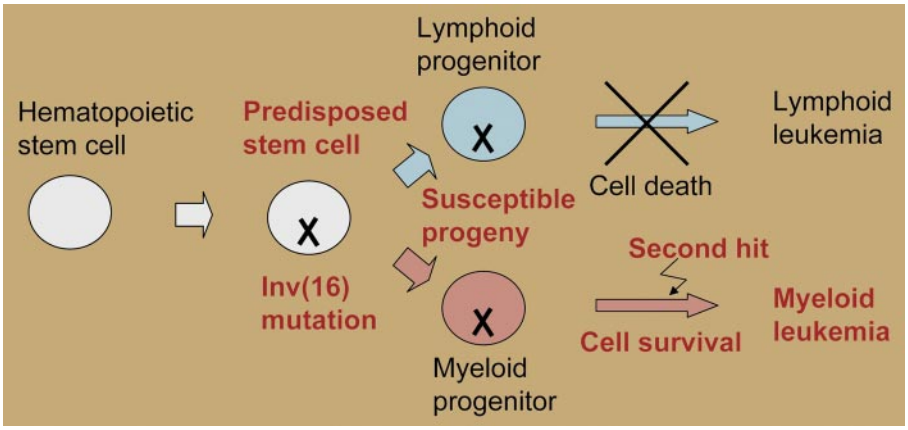
As the butterfly flaps its wings, so can a small latent change within hematopoietic cells have major effects on a pathological outcome such as leukemia.

The paper by Zhao and colleagues in this issue of *Blood* indicts a leukemia-related chimeric protein for selectively killing one cell type while sparing another to cause a cell type–specific disease.[1] The runt-related transcription factor 1 (RUNX1/AML1) and its cofactor core-binding factor subunit β (CBFβ) are essential regulators of hematopoiesis. Genetic



The CBFB-MYH11 butterfly effect. The Inv(16) mutation causes a latent lesion that decreases cell survival in lymphoid cells (blue) but not in myeloid cells (red).

defects including chromosomal translocations that affect *RUNX1* (t(8;21)) or *CBFB* (Inv16) genes have each been causally linked to the etiology of acute myelogenous leukemia. Both proteins are expressed in the myeloid and lymphoid lineages, yet pathological defects in RUNX1 or CBFβ function are evident only in the myeloid lineage. Why are the tumorigenic effects of RUNX1 and CBFβ lineage restricted? The spatiotemporal expression of RUNX1 and the extent of redundancy with other RUNX regulatory factors (eg, RUNX2 and RUNX3) could account in part for preferential effects in myeloid cells. However, CBFβ is ubiquitously expressed, and genetic aberrations that produce dominant-negative forms of CBFβ may affect normal myeloid growth and differentiation at any stage. The paper by Zhao and colleagues provides a cogent model to explain how a dominant-negative CBFβ protein causes tumors in the myeloid but not lymphoid lineage.

The CBFβ-SMMHC fusion protein is a prototypical dominant-negative factor, which is generated from the chimeric *CBFB-MYH11* gene as a result of the chromosome 16 inversion that is characteristic of human acute myeloid leukemia subtype M4Eo. The *CBFβ-SMMHC* related fusion protein inactivates RUNX1 and acts as an oncogene that promotes proliferation of immature myeloid progenitors. Mouse models based on CBFB-MYH11 have been effectively used to examine the roles of RUNX1 and CBFβ in hematopoiesis and progression of leukemia. Heterozygous expression of *Cbfb-MYH11* in a knock-in mouse model results in a phenotype similar to that of mice with complete loss of Runx1 or Cbfb.[2] Moreover, Lucio Castilla's group (Kuo et al[3]) showed that early expression of *Cbfb-MYH11* causes abnormalities in myeloid progenitors, thereby predisposing cells to leukemia. Recent studies by the research groups led by Nancy Speck (Zhao et al[1]) and Paul Liu (Talebian et al[4]) have revealed that, in addition to its role in myeloid differentiation, CBFβ is required for the T-lymphoid lineage.

Of importance, the chromosome 16 inversion occurs in hematopoietic stem cells, and thus the *CBFB-MYH11* fusion gene should affect both the lymphoid and myeloid lineages. In the current paper from Zhao and colleagues, T-cell development was examined in mice that express a conditional *Cbfb-MYH11* fusion gene, and the resulting phenotypes were compared with mice with severe Cbfb deficiency due to mutations generating null or hypomorphic alleles.[1] *Cbfb-MYH11* suppresses Cbfβ function at several stages of T-cell development. Hypomorphic mice with Cbfβ deficiency have a 20-fold reduction in thymocytes due to a differentiation block at the DN1 and DN2 stages. In contrast, *Cbfb-MYH11* knock-in chimeras are blocked at the DN1 stage of thymocyte development. Cre activation of the conditional *Cbfb-MYH11* knock-in reduces the number of adult thymocytes by an order of magnitude due to increased apoptosis of $CD4^+/CD8^+$ thymocytes. Consistent with these findings, the authors propose that the mechanistic basis for the association of *CBFB-MYH11* with myeloid leukemias rather than lymphoid leukemias is due to a molecular butterfly effect (see figure): cellular context determines that the fusion protein increases cell death in lymphoid cells, but does not decrease survival of myeloid cells that hence remain susceptible to secondary hits that cause leukemia.

The authors declare no competing financial interests. ■

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NEOPLASIA

Comment on Avet-Loiseau et al, page 3489

Multiple myeloma and FISH (but no CHIPS)

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Avet-Loiseau and colleagues present the definitive study of the clinical importance of genetic subtypes of multiple myeloma (MM).

These aberrations, detected by interphase fluorescence in situ hybridization (FISH), define subtypes of multiple myeloma (MM), each with different biology and prognosis and needing tailored management approaches. Avet-Loiseau and colleagues confirm the clinical relevance of genetic categories,[1] using the largest clinical data set reported to date: a cohort that is uniformly treated and has sufficient follow-up time. Two genetic categories