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# 1 **Desperately seeking a home marrow niche for T-cell acute lymphoblastic** 2 **Leukaemia**

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28 manuscript and gave important inputs.

29

## 30 **Abstract**

31 T-cell acute leukemia is a hematologic malignancy that results from the progressive  
32 acquisition of genomic abnormalities in T-cell progenitors/precursors. T-ALL is commonly  
33 thought to originate from the thymus albeit recent literature describes the possible  
34 acquisition of first oncogenic hits in hematopoietic progenitor cells of the bone marrow  
35 (BM). The journey of T-ALL from its arising to full blown expansion meets different  
36 microenvironments, including the BM in which leukemic cells settle down early after the  
37 disease spreading. We take advantage of recent literature to give an overview of important

38 cells and factors that participate in T-ALL, especially in the BM, arguing in favor of a home  
39 marrow niche for this rare leukemia.

40

#### 41 **Key words**

42 T-ALL, thymus, bone marrow, CXCL12, IL7, adipocytes.

43

#### 44 ***Introduction***

45 T-cell acute lymphoblastic leukaemia (T-ALL) constitutes a group of hematologic  
46 malignancies that result from the transformation of T cell progenitors. These pathologies  
47 concern children and adults. In the past twenty years, improvement in treatment protocols  
48 have contributed to a great amelioration of patient survival (Pui and Evans, 2013).  
49 Nevertheless, 15% of young patients and 45% of adults still relapse, which are of very bad  
50 prognosis (Litzow and Ferrando, 2015). Finding new ways to treat those patients is thus an  
51 important goal for ongoing research in the T-ALL field.

52 The knowledge accumulated from DNA sequencing and from functional T-ALL mouse models  
53 indicates that this blood disorder arises from the collaborative action of several oncogenic  
54 hits. Around 10-20 genomic abnormalities are the basis of this T-cell precursors'  
55 transformation (Girardi et al., 2017; Zhang et al., 2012). It is the accumulation of gain and  
56 loss of function of very diverse cell regulators that lead normal T cell precursors to lose their  
57 ability to fully differentiate into mature and functional T lymphocytes and to gain important  
58 survival and proliferative features, ultimately resulting in leukaemia (Belver and Ferrando,  
59 2016; Girardi et al., 2017) (Figure 1). It has long been admitted that T-ALL development  
60 occurs in the thymus where normal T cell differentiation takes place (Blom and Spits, 2006).  
61 Mouse models of early T-ALL development, using targeted oncogene expression in early T  
62 cells, such as in double negative (DN) CD4/CD8 thymocytes, have pointed these cells as  
63 putative cells of origin in certain T-ALL (McCormack et al., 2010; Tremblay et al., 2010).  
64 Experiments in which for instance LMO2 or LMO1 and TAL1 transcription factor expression  
65 was enforced in mouse DN3 T cell progenitors showed acquisition of self-renewal properties  
66 (Gerby et al., 2014; McCormack et al., 2010; Tremblay et al., 2010), and further  
67 transformation required additional genomic modifications, such as *Notch1*, *KRAS* or *NRAS*  
68 mutations, implicated in T cell engagement or in signal transduction pathways (García-  
69 Ramírez et al., 2018). In humans, the question relative to T-ALL pre-leukemic/cell of origin  
70 has been challenged using two main strategies. In one hand, enforced expression of

71 oncoproteins, such as NOTCH1/3, TLX3, TAL1/LMO2, in cord blood or bone marrow (BM)  
72 CD34<sup>+</sup> cells, forced to follow a T cell differentiation path using specific culture conditions or  
73 after transplantation in immune-deficient mice, was attempted as a way to dissect the early  
74 steps of T-ALL (De Smedt et al., 2002; García-Peydró et al., 2018; Pike-Overzet et al., 2007;  
75 Renou et al., 2017). Except for the work described in (García-Peydró et al., 2018), these  
76 attempts did not lead full blown leukaemia to develop, probably due to missing important  
77 secondary signals. However T cell progenitors accumulated as a result of a differentiation  
78 blockage and these progenitors were assimilated to pre-leukemic cells (De Smedt et al.,  
79 2002; Pike-Overzet et al., 2007; Renou et al., 2017). The second strategy, recently published,  
80 consisted in targeted sequencing of RNA from single hematopoietic CD34<sup>+</sup>CD38<sup>-</sup> progenitor  
81 cells sorted from the BM of T-ALL patients. The results indicated that in half T-ALL tested, a  
82 few multipotent cells held a hand of mutations found in leukemic cells, outlining the fact  
83 that these BM stem/progenitors may be cells of origin in human T-ALL (De Bie et al., 2018).  
84 As a matter of fact, as T-ALL progresses from the first genomic hit to the full spectrum of  
85 mutations and further expands to invade the body, the leukemic cells are in close contact  
86 with different microenvironments - thymus and blood infiltrated organs, including BM - that  
87 may impact their intrinsic behaviour as well as their chemo-sensitivity to treatments (Figure  
88 2).

89 Here we review the current knowledge of the relationships between the BM components  
90 and T-ALL. We especially focus our attention on late steps, when leukaemia has already  
91 spread in patient BM and blood. We question the current description of marrow niches of T-  
92 ALL.

93

#### 94 ***BM : a place to go for T-ALL?***

95 The diagnosis of leukaemia in patients copes with high infiltration rate of blood and BM  
96 (>20%), by immature looking blood cells. In the case of T-ALL, the blast cells originate from  
97 the thymus where progressive genetic abnormalities, such as translocation, gene fusion and  
98 mutations, have gradually accumulated in T cell precursors leading to uncontrolled cell  
99 growth, proliferation, survival and differentiation arrest to a point where undifferentiated  
100 highly proliferating cells start invading the whole organism (Girardi et al., 2017). How  
101 leukemic cells quit the thymus to disseminate to other body sites and whether there is a  
102 specific migration to the BM, is still unclear (Passaro et al., 2016; Vadillo et al., 2018). What

103 is much well known is how normal T cells transit within the thymus, from cortex to medulla,  
104 as they mature and how they eventually exit towards the blood when they reach their final  
105 differentiation stage (James et al., 2018). Upregulation of surface receptors such as CC-  
106 chemokine receptor 7 (CCR7) and expression of Semaphorin 3E receptor PlexinD1 are crucial  
107 to the T cell precursors from the thymic cortex to enter the medulla rich area following a  
108 gradient of CCR7-ligands CCL19 and CCL21 and thus further progress in the differentiation  
109 (Choi et al., 2008; Kwan and Killeen, 2004; Ueno et al., 2004). In later T cell differentiation  
110 stages, differential expression of CD69, CD62L and sphingosine-1-phosphate receptor 1  
111 (S1PR1) allows mature T cells to leave the thymus and reach the blood circulation. Finely  
112 tuned S1P levels, the ligand of S1PR1, are necessary to avoid intrathymic accumulation of  
113 newly produced mature T cells, that is orchestrated by different cells, such as thymic  
114 epithelial, stromal and endothelial cells, the latest being the gate keeper between the  
115 thymic microenvironment and the blood circulation (James et al., 2018). Because T-ALL cells  
116 are mostly restricted to pre-cortical or cortical precursors, i.e. that did not underwent  
117 sufficient differentiation to achieve the passage in the medulla, one can expect that  
118 mechanisms driving T-ALL emigration out of the thymus may involve molecules that are  
119 detected in the early steps of differentiation. CCR7 does not seem to be crucial in this  
120 phenomenon since deletion of CCR7 did not hamper Notch1-induced T-ALL migration,  
121 development and propagation. Only central nervous system invasion by T-ALL was modified  
122 in absence of CCR7 (Buonamici et al., 2009) albeit this result is debated (Jost et al., 2016).  
123 The chemokine receptor CXCR4 is widely expressed in newly diagnosed human T-ALL and in  
124 mouse models (Pitt et al., 2015) (*and our own results*) and its ligand CXCL12 is predominantly  
125 produced by the thymic cortex, and not by the medulla (Lucas et al., 2017). Albeit the role of  
126 CXCR4 in mature T cells exit from the thymus is debated (James et al., 2018), one may  
127 hypothesize that as leukaemia expands in the thymic cortex, a shortage in CXCL12 due to  
128 high consumption by pre-leukemic/leukemic cells may allow the “unfed” ones to start  
129 leaving the thymic environment and to find a lodgement in secondary CXCL12 producing  
130 niches, such as the BM. This “consumption” mechanism has been proposed to explain why  
131 the level of Interleukin 7 (IL7) is lower in the plasma of T-ALL patients compared to controls  
132 (Silva et al., 2011) as previous analyses showed IL7 circulating levels may be regulated by  
133 consumption (Park et al., 2004). Treatment of mice with the CXCR4 antagonist AMD3100  
134 redistributes leukocytes from primary immune organs, such as thymus and BM, to secondary

135 immune organs (Liu et al., 2015) indicating that preventing CXCR4 activation helps T cells to  
136 detach and recirculate. In the same idea, it is reported that T-ALL expansion perturbs the  
137 thymus architecture (García-Ramírez et al., 2018). In this context, cortical thymic epithelial  
138 cells (cTECs) may progressively be lost as a consequence of T-ALL intra-thymic development  
139 and because cTECs are CXCL12 producing cells (Lucas et al., 2017), their shortage during  
140 disease development may also lead to decreased levels of local consumable CXCL12 and help  
141 T-ALL cells to egress from the thymus.

142

### 143 ***BM: a place to be for T-ALL?***

144 BM is a major site in which T-ALL leukemic cells are detected during the leukaemia process  
145 and after their intra-venous transplantation in mouse recipients (De Keersmaecker et al.,  
146 2010; Hawkins et al., 2016; Passaro et al., 2015; Poglio et al., 2016). Getting into the BM  
147 microenvironment requires many steps such as adhesion on endothelial cells and  
148 extravasation from the blood circulation to enter the bone cavity. Albeit these mechanisms  
149 are well described for normal patrolling T cells that enter lymph nodes, precise information  
150 is missing for T-ALL when invading the BM (Vadillo et al., 2018). Once in the BM, leukemic  
151 cells need to find a proper niche among the very diverse BM microenvironment that would  
152 allow them to survive and proliferate (Morrison and Scadden, 2014). Recent studies have  
153 described the localization of T-ALL cells close to BM perivascular stromal and vascular cells  
154 shortly after leukemic cell injection (Pitt et al., 2015). Even though vascular endothelial cells  
155 (VEC) are not the main source of CXCL12 in the BM (Ding and Morrison, 2013; Greenbaum et  
156 al., 2013; Tikhonova et al., 2019), Pitt and colleagues demonstrated that CXCL12 specifically  
157 produced by VEC is necessary for the maintenance and progression of T-ALL *in vivo* (Pitt et  
158 al., 2015). These results remind the role of VEC-derived CXCL12 in maintaining  
159 hematopoietic stem cells (HSC) but were unexpected given that osteoblasts constitute a  
160 niche for lymphoid progenitors in BM (Ding and Morrison, 2013; Greenbaum et al., 2013).  
161 Conditional deletion of CXCL12 in VEC or treatment with a CXCR4 antagonist significantly  
162 decreased T-ALL propagation, indicating that VEC and production of CXCL12 are important  
163 for T-ALL development once BM is reached (Pitt et al., 2015). This observation fits with  
164 another study that showed an impact of CXCL12/CXCR4 in T-ALL migration, survival and  
165 expansion (Passaro et al., 2015). However, a more recent study that surveyed T-ALL  
166 localization close to osteoblasts, perivascular mesenchymal stem/progenitor cells and

167 vasculature using intra-vital microscopy, reported stochastic distribution of leukemic cells  
168 relative to these three cell BM components, rather than stable niche, and a high motility  
169 rarely restricted to the vicinity of any specific cell types or structures (Hawkins et al., 2016).  
170 These controversial results are not explained by the leukemic models studied, as similar  
171 oncogenic activation was used to induce T-ALL from mouse progenitors and human T-ALL  
172 were as well studied in both works. One main difference is the mouse BM location in which  
173 T-ALL initiation was explored, tibia vs calvaria (Hawkins et al., 2016; Pitt et al., 2015), which  
174 may imprint different behaviour to leukemic cells. A previous report showed substantial  
175 heterogeneity between calvaria and epiphyses and diaphysis of long bones in terms of bone  
176 remodelling activity, blood volume fraction and hypoxia (Lassailly et al., 2013). T-ALL are also  
177 very much dependent on a specific cytokine, that is IL7 (Barata et al., 2004, 2001). IL7 is  
178 crucial for normal T cell development and the expression of its receptor, IL7R $\alpha$ /CD127,  
179 varies in thymocytes according to the differentiation stages, being high in early T cells, lower  
180 in DP CD4<sup>+</sup>CD8<sup>+</sup> and re-induced in late SP mature T cells in accordance with the production  
181 of IL7 by cTECs (Akashi et al., 1998; James et al., 2018; Plum et al., 1996). So it is not  
182 surprising that about 70% of T-ALL, that are precursor T cells, express IL7R and respond to  
183 IL7 (Barata et al., 2004; Karawajew et al., 2000). *In vitro*, IL7 is a major cytokine to add in  
184 culture medium to grow T-ALL from patients (Armstrong et al., 2009; Scupoli et al., 2003;  
185 Yost et al., 2013) and recent development of a human anti- IL7R $\alpha$  antibody indicated  
186 efficient leukaemia cytotoxicity *in vitro* and delayed T-ALL development *in vivo* (Akkapeddi et  
187 al., 2019). Interestingly IL7/IL7R interaction does not similarly drive the activation of  
188 downstream STAT5, PI3K/Akt/mTOR and MEK/Erk pathways in normal and malignant states  
189 (Oliveira et al., 2019), indicating specific targeting of leukemic cells may be found. Notch  
190 activation, another important Receptor/ligand pathway in normal T cell differentiation  
191 (Radtke et al., 2010), is also implicated in T-ALL development, propagation and maintenance  
192 (Armstrong et al., 2009; Weng et al., 2004). It is expressed concomitantly to IL7/IL7R in the  
193 thymus compartments where they cooperate to induce proliferation of T cell progenitors  
194 while suppressing their non-T cell fates (García-Peydró et al., 2006), in relation with the fact  
195 that Notch1 signalling drives IL7R $\alpha$  expression in early T cells and leukaemia (González-  
196 García et al., 2009). Importantly, both *Notch1* and *IL7R $\alpha$*  genes are targeted by gain of  
197 function mutations in T-ALL patients (Weng et al., 2004; Zenatti et al., 2011) further outlining  
198 the importance of both signalling pathways in supporting leukemia survival/expansion. Of

199 note, *Notch1* mutations appear late during the oncogenic process, indicating only  
200 cooperative effect with other premium genomic abnormalities (De Bie et al., 2018). Notch  
201 ligands Delta-like 1 and Delta-like 4 (DLL1, DLL4) that are the major ligands of Notch1  
202 implicated in thymic T cell development, and IL7 are produced by different cells of the BM  
203 microenvironment. Indeed, single cell RNA sequencing analyses identified VE-cadherin  
204 positive endothelial cells as the exclusive DLL1/DLL4 expressing BM non-hematopoietic cells  
205 whereas IL7 is detected in Leptin receptor positive (LepR<sup>+</sup>) mesenchymal stromal/stem cells  
206 (MSC) (Baryawno et al., 2019; Tikhonova et al., 2019). DLL4 that has also been detected in  
207 osteoblastic cells (Yu et al., 2015) induces T-ALL expansion *in vitro* and *in vivo* (Minuzzo et al.,  
208 2015). Interestingly, CXCL12 is much more broadly expressed than the Notch ligands  
209 DLL4/DLL1 and IL7, but its highest expression is detected in LepR<sup>+</sup> cells that also produce IL7  
210 (Tikhonova et al., 2019). This observation is supported by a recent paper describing the  
211 coincident production of IL7 and CXCL12 by unique peri-sinusoidal stromal cells, that  
212 aggregate pro-B cells and HSC at very close spots, representing another potential cellular  
213 niche for T-ALL (Balzano et al., 2019). Other growth factors/cytokines have been shown to  
214 help T-ALL to propagate. Insulin-growth factor 1 (IGF1) is one of them and its receptor is  
215 broadly expressed in T-ALL as a result of Notch1 activation (Medyouf et al., 2011) whereas  
216 transcripts of IGF1 are detected almost exclusively in osteoblastic cells (Tikhonova et al.,  
217 2019). Blocking or deleting IGF1 receptor in mouse T-ALL has major effects in the  
218 progression of leukemia *in vivo* with low leukemia-initiating activity being observed in such  
219 conditions (Medyouf et al., 2011). Interestingly, T-ALL can also contribute to its own growth  
220 through education of dendritic cells to secrete high IGF1 levels (Triplett et al., 2016).  
221 Speaking about cross-talks between the BM and T-ALL, an interesting finding concerns the  
222 implication of the pro-inflammatory cytokine, IL18, in T-ALL propagation. Indeed, a recent  
223 study described the presence of enhanced IL18 levels in the circulation of T-ALL patients  
224 (Uzan et al., 2014). IL18 receptor is expressed in T-ALL cells and interfering with its  
225 expression using a shRNA approach as well as blocking IL18 with a neutralizing antibody or  
226 using knock-out mice, greatly limits leukemia expansion in mouse and human T-ALL models  
227 (Uzan et al., 2014). IL18 is not produced by leukemic cells but rather by endogenous BM  
228 cells, including stromal cells (Uzan et al., 2014). Single cell RNA seq identified few IL18  
229 expressing cells among LepR<sup>+</sup> stromal cells, indicating potential overlap with IL7 and CXCL12  
230 producing cells (<http://aifantislabs.com/niche> from (Tikhonova et al., 2019). As a sum up, T-ALL



231 cells that home to BM can count on many different local interactions to help their growth  
232 and propagation, providing mechanistic clues on why the BM is a “warm nest” for this  
233 leukaemia (Figure 3).

234

### 235 ***BM, BM... which BM are you talking about?***

236 BM niches are numerous and very diverse in the human body, partly due to the architecture  
237 of the different bones. With aging, the BM composition changes and marrow niches become  
238 more and more infiltrated with adipose tissue; in the neonate, the BM is entirely  
239 hematopoietic and during the first year of life the conversion from hematopoietic, or red, to  
240 fatty, or yellow, marrow begins (Vogler and Murphy, 1988). The completion time of  
241 hematopoietic to adipocytic conversion is different if one considers the appendicular and  
242 the axial skeleton, the latest proceeds throughout life whereas the first one is over by the  
243 time of skeletal maturity (Laor and Jaramillo, 2009). Moreover the red to yellow marrow  
244 conversion follows a very specific pattern starting distally at the phalanges and moving  
245 centrally towards the axial skeleton. In bones such as humerus, sternum and clavicle, fatty  
246 transformation starts in the epiphysis, proceeds through the diaphysis and ends in the  
247 metaphysis (Zawin and Jaramillo, 1993). Thus looking at BM niches in a given (long) bone, at  
248 young adult time, in mouse, may only provide a limited, even though very informative,  
249 portray of the BM microenvironment at steady state or upon stressful conditions, such as  
250 after chemical myeloablation or after leukaemia development (Baryawno et al., 2019;  
251 Tikhonova et al., 2019; Zhou et al., 2017), and not taking into account the evident man to  
252 mouse bone architecture differences. With this caveats in mind, one may question whether  
253 the leukemic cells behave similarly in different bones, where for instance the BM red to  
254 yellow conversion state is not at the same levels. This question is important because BM  
255 adipocytes are known as modulators of BM cell components, such as osteoblastic and  
256 hematopoietic cells (Ambrosi et al., 2017). Interestingly a recent study investigated the  
257 metabolic and cell cycle state of T-ALL recovered from two different fat-containing mouse  
258 BM sites, i.e. thoracic and tail vertebrae, in mouse and xenograft models. Compared to  
259 thoracic/red BM, T-ALL cells from tail vertebrae/yellow BM were in a lower metabolic and  
260 quiescent state that correlated with higher T-ALL intrinsic chemoresistance to cell cycle-  
261 targeting drugs (Cahu et al., 2017). This state was reversible upon cultures in permissive  
262 conditions and after secondary transplants, as leukemic cells reached long bones/red BM

263 areas (Cahu et al., 2017). Albeit the exact mechanisms depicting the effect of the adipocyte-  
264 rich BM on T-ALL are currently unknown, these results are in line with recent analyses  
265 showing that BM adipocytes are negative regulators of the hematopoietic  
266 microenvironment (Naveiras et al., 2009). However, more recent studies showed that  
267 hematopoietic recovery after myeloablation is supported by BM adipocytes from long bones  
268 but not from caudal vertebrae that seem to influence not only hematopoiesis but also BM  
269 vascularization (Zhou et al., 2017). These last results indicate an even higher degree of  
270 variability between the BM cell content, even for well-known adipocyte lineage, of different  
271 bones, outlining the difficulties of understanding the exact relationship between leukaemia  
272 and its microenvironment in bones. The study of leukaemia development in tail and thorax  
273 vertebrae also pinpoints the fact that when leukaemia treatment efficiency is assessed by  
274 BM aspiration in a defined bone spot, one may not forget that other infiltrated bones may  
275 provide another reality.

276

### 277 ***BM and T-ALL marriage: not yet concluded?***

278 Considering the signals available in the BM, it is thus expected that T-ALL are to go and stay  
279 in the medullary niches, some of them supporting chemoresistance during treatments. *Ex-*  
280 *vivo* experiments have shown that T-ALL in contact with MSC have low reactive oxygen  
281 species (ROS), in relation with enhanced mitochondrial fragmentation. Low ROS levels  
282 participate in MSC-mediated T-ALL resistance to aracytin and methotrexate (Cai et al., 2016).  
283 It has also been observed that leukemic cells may transfer mitochondria to MSC in presence  
284 of these drugs through intercellular nanotube formation, and this phenomenon decreases  
285 ROS levels in leukemic cells, similarly contributing to chemo resistance (Wang et al., 2018).  
286 Nevertheless, as mentioned earlier in the text, T-ALL cells, like grasshoppers in a fertile field,  
287 can devastate and reduce cell diversity. Studies have shown that in T-ALL invaded BM,  
288 osteoblasts disappear as a consequence of aberrant activation of Notch1 in osteoblastic  
289 progenitors, and this coincides with HSC/progenitor functional loss (Hawkins et al., 2016;  
290 Wang et al., 2016). Moreover, MSC isolated from the BM of T-ALL patients become  
291 senescent and are unable to differentiate into adipocytes, osteocytes and chondrocytes (Lim  
292 et al., 2016), a state that may be linked to massive mitochondrial transfer from leukemic  
293 cells to MSC (Wang et al., 2018). Interestingly, a similar mechanism was described to explain

294 HSC protection from senescence in the BM niche, e.g. a direct transfer of ROS mediated by  
295 Connexin-43 from HSC to BM stromal cells (Taniguchi Ishikawa et al., 2012).  
296 The remaining burning question is whether the “grasshopper effect” of T-ALL, that may not  
297 be restricted to this leukemia type, is totally reversible. Indeed, elimination of leukemic cells  
298 from the BM by chemotherapeutic agents may not fully restore the normal BM  
299 microenvironment supporting properties, leading to dysfunctional long term production of  
300 hematopoietic cells.

301

### 302 ***That’s all folks!***

303 Much efforts have been produced to understand the reciprocal relations between BM  
304 microenvironment and T-ALL in the recent years. The current results provide a still  
305 preliminary picture of the cell/factors exchanges that may be refined with the recent  
306 development of single cell analyses and of very precise intra-vital microscopy. Questions  
307 relative to the chemoprotection of leukemic cells by the diverse BM microenvironments are  
308 still pending but will undoubtedly be resolved in a near future. This may open to  
309 complementary strategies to target resistant cells in their home marrow nest.

310

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312

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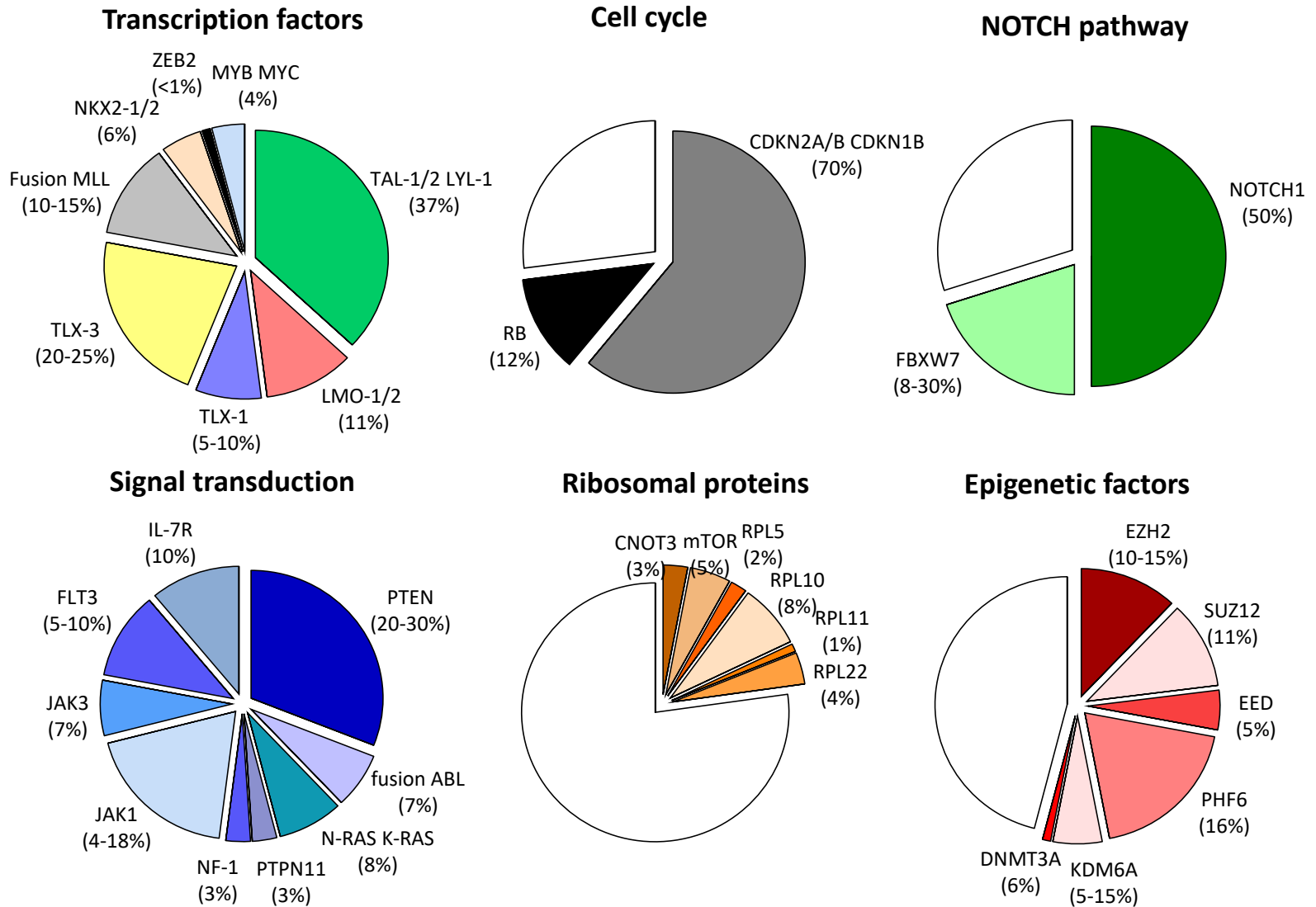
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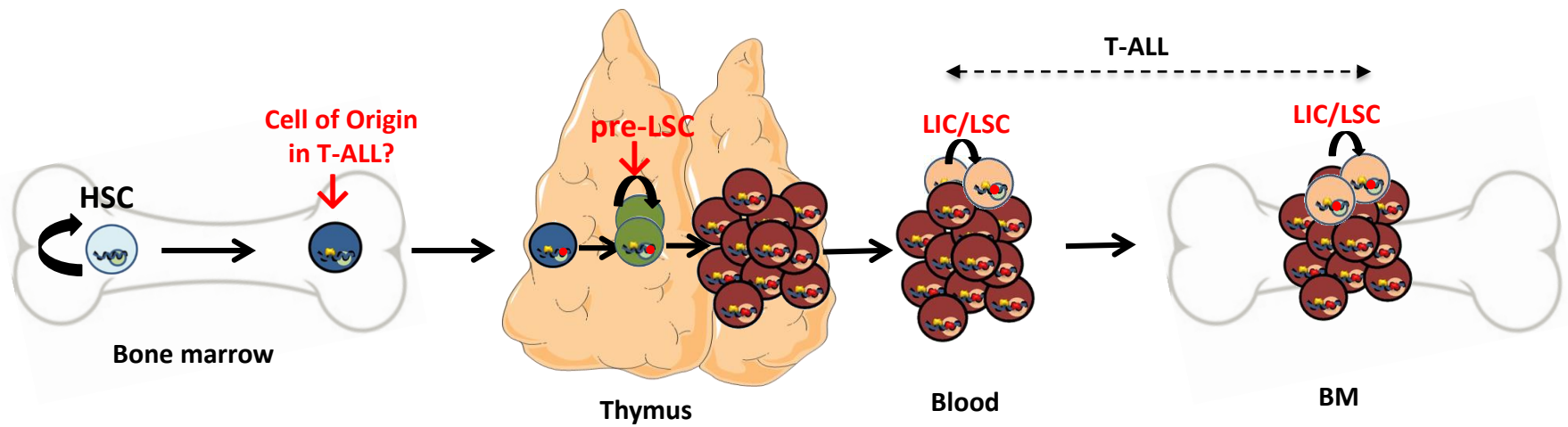
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**Figure 1: Classification and frequencies of the main molecular targets of oncogenic abnormalities in T-ALL. Shown are the different factors distributed in categories being more or less frequently affected in leukemic cells**



**Figure 2:** Simplified model of T-ALL development starting in the BM, proceeding in the thymus and further invading BM again (adapted from [Garcia Ramirez I. et al, Embo J., 2018](#)).

Mesenchymal stem/stromal cells  
(vascular perisinusoidal)

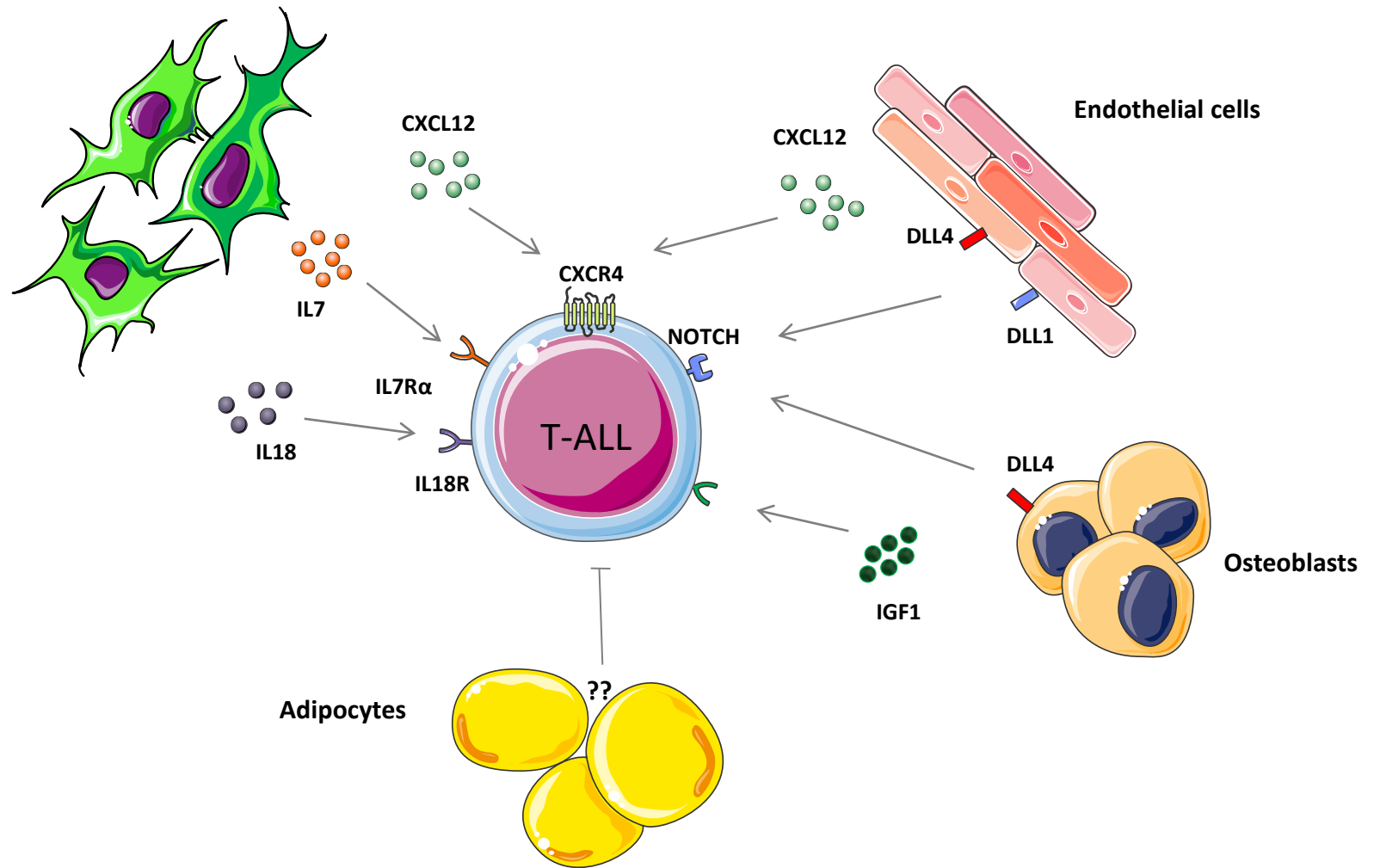


Figure 3: Overview of extrinsic factors and non-hematopoietic BM cells known to regulate T-ALL (from Pitt *et al.*, 2015, Passaro *et al.*, 2015; Armstrong *et al.*, 2009; Tikhonova *et al.*, 2019; Cahu *et al.*, 2017; Balzano *et al.*, 2019; Medyouf *et al.*, 2011; Passaro *et al.*, 2015; Silva *et al.*, 2011; Uzan *et al.*, 2014; Baryoawno *et al.*, 2019)