The unexpected and unresolved roles of PDGFRA and PDGFRB in T-cell acute lymphoblastic leukemia

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Received: January 26, 2024.
Accepted: February 15, 2024.
Early view: February 22, 2024.

https://doi.org/10.3324/haematol.2023.284524

Platelet-derived growth factor (PDGF) has been investigated for over 50 years. Despite the numerous detailed studies about the PDGF growth factors and their receptors, PDGFRA and PDGFRB, in health and disease, new findings, such as those reported by the group of Pieter Van Vlierberghe in this issue of *Haematologica*,[1] keep surprising us about the diverse roles of these receptors in various cancers.

The platelet-derived growth factor receptor (PDGFR) family comprises a group of receptor tyrosine kinases with a characteristic split kinase domain. For the fascinating story about the discovery and cloning of PDGF and its receptors in the 1970s and 1980s, we refer to the review article by Bowen-Pope and Raines.[2] Interestingly, the PDGFR family does not only include PDGFRα and PDGFRβ, but also FLT3, KIT and the CSF1R receptors, which all have very similar structures. Ligand binding causes homo- or heterodimerization of the receptor, which activates the kinase domains and leads to phosphorylation of the receptors, as well as a variety of signaling proteins.[3]

All of these receptors are implicated in cancer development, either by being directly mutated and actively driving cancer development or by a role in angiogenesis, one of the hallmarks of solid tumors. The *PDGFRA*, *PDGFRB*, *FLT3* and *KIT* genes are now well known for their roles in various hematologic malignancies. The *ETV6-PDGFRB* fusion gene was one of the first identified oncogenes in this family in myeloid neoplasms often associated with eosinophilia.[4] Since then, many other *PDGFRB* fusions have been identified with numerous fusion partners. Later, internal tandem duplications (ITD) were observed in *FLT3* in AML, *KIT* mutations were identified in systemic mastocytosis, and the *FIP1L1-PDGFRA* fusion was identified as a cryptic but recurrent fusion gene in chronic eosinophilic leukemia.[5-7] In solid tumors, *PDGFRA* or *PDGFRB* amplification / overexpression are often found, and in gastro-intestinal tumors mutant *PDGFRA* or mutant *KIT* are important oncogenic drivers.[8]

In acute lymphoblastic leukemia (ALL), however, *PDGFRA* or *PDGFRB* alterations have as yet only been detected in few isolated cases, including in Ph-like ALL and in a few T-ALL cases.[9,10]

In a recent issue of *Haematologica*, the group of Pieter Van Vlierberghe identified an *MYH9-PDGFRB* fusion gene in one case of T-lymphoblastic lymphoma (T-LBL). Moreover, upon subsequent further exploration in T-ALL, they identified expression and phosphorylation of PDGFRβ in several T-ALL cases.[1] Surprisingly, another group recently described PDGFRA fusion genes in relapsed / refractory T-ALL.[11] Although there had been some previous indications that PDGFRA/B could be rearranged in T-cell malignancies, these recent studies definitively identify activated PDGFRα and PDGFRβ as drivers of T-ALL and T-LBL, and as possible therapeutic targets in T-cell malignancies.

In the study of the Van Vlierberghe group, the authors initially studied the oncogenic potential of MYH9-PDGFRβ in cell and mouse models.[1] In line with previous reports on PDGFRβ fusion proteins, MYH9-PDGFRβ showed auto-phosphorylation, activation of downstream signaling proteins such as STAT5, and transformed Ba/F3 cells to growth factor independent growth. In addition, expression of this fusion gene in bone marrow cells of mice resulted in the rapid development of myeloid or T-cell malignancies with accumulation of $Gr1^+/Cd11b^+$ myeloid cells or $Cd4^+/Cd8^+$ lymphoid cells, respectively. The development of both myeloid and lymphoid malignancies in the mouse model is similar to what has been observed with other oncogenic tyrosine kinases and is also dependent on the mouse strain that is used. Finally, the authors also demonstrated efficacy of a selective PDGFRβ inhibitor to reduce the leukemia burden *in vivo* using a patient-derived T-ALL xenograft model with a T-ALL sample that showed PDGFRβ activation.

Surprisingly, further analysis of T-ALL PDX samples by western blotting revealed expression and phosphorylation of PDGFRβ in 4 of 11 T-ALL cases.[1] Intriguingly, the exact

cause of the elevated PDGFRβ protein levels and auto-phosphorylation could not be attributed to mutations or other obvious genomic changes, and this, therefore, remains to be solved. These elevated PDGFRβ protein levels may not always be detectable at RNA level and could thus be missed if only RNA-seq data are analyzed. Further studies are warranted to explore the sensitivity of T-ALL cases to PDGFRβ inhibitors. Moreover, in an independent study by Paolino *et al.* on relapsed / refractory T-ALL/T-LBL cases, these authors identified 3 of 14 cases with alterations of the *PDGFRA* gene.[11] Here they found 2 cases with the *FIP1L1-PDGFRA* fusion and one case with the D842V mutation in *PDGFRA*.

These recurrent *PDGFRA* and *PDGFRB* aberrations in T-ALL/T-LBL indicate that existing PDGFR kinase inhibitors could be tested in relapsed cases for which no other effective therapies exist.[1,11] Imatinib is the oldest inhibitor (already off patent) that could be explored, since this inhibitor is well tolerated and is a very potent PDGFR kinase inhibitor.[7] However, it is already known that the D842V mutation in PDGFRα causes resistance to imatinib, and in such cases sorafenib or other newer kinase inhibitors are needed.[8]

This work was initiated by Pieter Van Vlierberghe, but unfortunately he did not get the chance to complete the study and witness how this work could influence further research and be applied in the clinic.[12] Pieter was an extraordinary scientist and a very committed collaborator. He would do the impossible to contribute to other projects worldwide. Advancing T-ALL research to improve patient care was close to his heart.

As also demonstrated in this study here,[1] Pieter had a talent for identifying unique leukemia cases with interesting genomic alterations and then start from such observations to study them in larger cohorts. This work often led to fantastic new discoveries, such as the identification of the *PHF6* mutations in T-ALL. In that work, Pieter started from a few isolated cases with *PHF6* deletions and finally discovered that *PHF6* is one of the most frequently mutated genes in T-ALL.[13]

It is now more than a year ago that Pieter passed away after a courageous fight over several years during which he remained active in the field, contributed to studies, led his own research lab, and obtained research funding. He was a 'warrior', a 'soldier', and a 'champion', as in the lyrics of one of his favorite songs by 'Oscar and the Wolf'. "They say that I'm gonna be a star one day". We all miss him so much, but his contribution to T-ALL research and clinical practice is continuing to make changes and will do so forever.

Disclosures

No conflicts of interest to disclose.

Contributions

KV and JC analyzed the literature and wrote the manuscript.

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