Leukemia (1999) 13, Suppl. 1, S96

http://www.stockton-press.co.uk/leu

BCR/ABL rearrangement and leukemia phenotype

G Saglio[1], F Pane[2], G Martinelli[3] and A Guerrasio[4]

[1]*Clinica Medica, Universita' di Torino, Ospedale Maggiore della Carita', Novara;* [2]*CEINGE-Biotecnologie Avanzate and Dipartimento di Biochimica e Biotecnologie Mediche, Universita' 'Federico II', Napoli;* [3]*Istituto di Ematologia 'L & A Seragnoli', Universita' di Bologna, Bologna; and* [4]*Dipartimento di Scienze Biomediche ed Oncologia Umana, Universita' di Torino, Ospedale S Luigi Gonzaga, Orbassano, Torino, Italy*

Since the discovery that Philadelphia chromosome translocation is characterized, at the molecular level, by different types of BCR/ABL gene rearrangements, the issue of the relationship between the hybrid gene structure and the disease phenotype has puzzled clinical and molecular hematologists. Notwithstanding the body of data accumulated in the last few years, this issue is at present largely unsettled. However, recent observations contributed to fill some gaps in the picture unravelling new links between molecular structure and clinical features.

A comprehensive view of the different BCR/ABL hybrid transcripts and proteins so far detected in human leukemias is outlined in Table 1. In almost all cases of CML the larger BCR/ABL fusion protein P210 is found (Kurzrock R *et al. New Engl J Med* 1988; **319**: 990); however, in very few CML cases only the shorter P190 (Selleri I *et al. Blood* 1990; **75**: 1146) or the elongated P230 hybrid proteins were detected (Saglio G *et al. Blood* 1990; **76**: 1819). In all cases, while the ABL counterpart of the rearranged gene is the same as P210, a variable amount of the BCR coding sequences are included in the hybrid gene. At first glance P190 and P230 CMLs do not seem clinically different from classical P210 form, but a more keen insight into patients' clinical and hematological profile revealed some distinguished features: P190 CMLs show a peripheral monocytosis overlapping to some extent the CMML picture (Melo JV *et al. Leukemia* 1994; **8**: 208), whereas P230 CMLs peripheral smear is more similar to CNL (Pane F *et al. Blood* 1996; **88**: 2410). Finally a CML molecular variant with a fusion protein of intermediate size between P210 and P190 has been recently described (Hochhaus A *et al. Blood* 1996; **88**: 2236). The overall picture is further complicated by the discovery that all P210 CMLs express at diagnosis some amount of P190 (Saglio G *et al. Blood* 1996; **87**: 1075; van Rhee *et al. Blood* 1996; **87**: 5213); at present the exact meaning of this unexpected finding, originated by an alternative splicing of BCR/ABL message, is not enterely clear: recent data suggest that the level of P210 and P190-type transcripts are mutually correlated (Mostarda I *et al. Exp Hematol* 1996; **24**: 1133). Indeed, high levels of both transcripts are observed during blastic transformation of CML, whereas hematologic remission induced by α-IFN therapy is usually associated with a low level of P210 transcript; in these cases P190 transcript is frequently severely reduced or undetectable (ibid). The above data point out that, besides qualitative differences, quantitative variations of BCR/ABL transcripts level may play a role in dictating the disease phenotype.

Table 1 BCR-ABL hybrid transcripts and proteins in Ph+ human leukemias

Hybrid transcripts	*Fusion proteins*	*Leukemic phenotype*
e1/a2	P190	ALL, CMML-like CML, AML M4-M5
e6/a2	>P190	CML
b2a2, b3a2	P210	CML, ALL
c3a2	P230	CNL-like CML

a2, ABL exon 2; e1, e6, b2, b3, c3, BCR exons; CML, chronic myeloid leukemia; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; M4, M5, FAB classification of AML; CMML, chronic myelomonocytic leukemia; CNL, chronic neutrophilic leukemia; >P190, protein larger than 190 kDa.

About 70% of Ph+ ALL cases bear the P190 fusion protein which is endowed with a higher transforming activity than P210 (Lugo TG *et al. Science* 1990; **247**: 1079); however, in nearly 50% of adult cases only the P210 hybrid protein is found, thus overlapping exactly the molecular rearrangement of CML. Indeed the most intriguing question of the BCR/ABL puzzle is represented by the fact that the same oncogenic protein (P210) seems able to induce both a chronic leukemia with myeloid lineage proliferation and differentiation and an acute lymphoid leukemia of B cell origin. Albeit some cases of P210 ALL probably represent early lymphoid blast crisis of CML whose chronic phase was clinically unnoticed, this is not true for the majority of P210 ALLs whose clinical profile is more typical of a *de novo* acute leukemia. On the other hand, the above reported cases of P190 CML and the presence of variable amount of P190 in every case of CML, suggest that the presence of P190 protein is not *per se* able to induce an acute leukemic phenotype. Nevertheless *in vitro* and animal studies have pointed out that P210 and P190 possess different oncogenic potency and cause distinct types of leukemia in transgenic mice (Voncken JW *et al. Blood* 1995; **86**: 4603) but share the same target cell specificity (Kelliher M *et al. Mol Cell Biol* 1991; **11**: 4710). At present, the mechanisms underlying the above observed discrepancies are unknown; but we can speculate that additional genetic alterations, so far undetected, could be responsible for the observed phenotype. Alternatively, more subtle quantitative differences in P190 and P210 expression or in the P190/P210 ratio at cellular level could have a major impact on the leukemia phenotype. Hopefully, quantitative analysis of the BCR/ABL transcripts, now feasible with new technical approaches, could contribute to settle this clinical–molecular enigma.