Chronic Myelogenous Leukaemia: Philadelphia chromosome and its molecular implication

Chronic Myelogenous leukaemia (CML), or chronic granulocytic leukaemia (CGL), is a cancer of white blood cells where myeloid cells proliferate via unregulated growth in bone marrow. Uncontrolled proliferation of myeloid cells and its descending cells uses up constructive metabolites, resulting in a lack of other normal blood cells which leads to leukemic clinical symptoms.

Progress in the etiology of CML

CML was first observed associated with a chromosomal abnormality. (Nowell P.C. and Hungerford , 1960) An unusual small chromosome was observed in CML cells from different patients, termed Philadelphia chromosome (Ph), which was later identified to have derived from chromosome 22. The poor morphology of metaphase chromosome from human CML hampered the research using karyotyping technology. The chromosomal anomaly was viewed as a deletion from chromosome 22 until in 1973, Rowley showed that the deleted part of chromosome 22 was actually present on chromosome 9 using newly-developed quinacrine fluorescence and Giemsa staining, identifying this anomaly as a translocation between chromosome 22q and 9q, reads t(9;22)(q34;q11).

The organization of Ph translocation was later assessed using human-rodent cellular fusion to a more detailed level. Pre-identified proto-oncogenes *c-ABL*, a cellular homolog of Abelson murine leukaemia oncogene) and *c-SIS* (mammalian homolog of simian sarcoma virus oncogene), were showed to be transposed to the opposite chromosome (Annelies de Klein et al, 1982). At that time, it was hypothesised that the dissociation of a specific gene from its promoter, perhaps a following fusion to a cellular promote, results in overexpression of its gene product that leads to malignant transformation. It is shown later that c-*SIS* is located on 22q12.3-13.1, not proximal to the breakpoint within *bcr* on 22q11 (Bartram et al,1984). This fact excludes involvement of *SIS* in CML.

Further gene mapping shows that the breakpoints are within c-*ABL* on 9q and *bcr* (Breakpoint cluster region, later found to be located within a protein-coding gene then named *BCR*) on 22q employing cDNA probe and K562 cell line (Heisterkamp et al, 1985, Groffen et al, 1984). An unusual mRNA transcript was detected hybridizing to both c-*ABL* probe and *BCR* probe, suggesting a *BCR-ABL* fusion gene resulted from translocation (G. Grosveld et al,1986) , which is later well established. The *BCR-ABL* is invariably detected in CML patients with or without an apparent Ph chromosome (Kurzrock R. et al, 1988), demonstrating a highly specific association with CML. Using transgenic mice models, expression of BCR-ABL is shown to cause disease course. More than 50% of transgenic mice expressing $P190^{BCR/ABL}$ developed pre-B leukaemia/lymphoma, resembling ALL and CML in human, before they reach age of 6 months (Groffen J. et al. 1992),suggesting that expression of BCR-ABL causes malignancy transformation in blood cells.

It was notable that many other oncogenes are each involved in their characteristic constitutive chromosomal anomalies to result in cellular transformation towards malignancy causing cancer (See Table 1), suggesting that the result revealed in Ph translocation would shed light on mechanism of other cancers.

Table1 (AG van Kessel, 1983)

Cellular oncogenes, their chromosomal localization and the involvement of these chromosomes in Karyotypic changes in certain neoplastic disease

Oncogene	Virus strain	Human chromosome localization	Chromosome aberration	Disease[xx]	Reference
c-myb	Avian myloblastosis virus	6(q22-q24)	6q-	ALL	1.2
c-mos	Moloney murine sarcoma virus	8(q22)	t(8;21)(q22;q22)	AML	3.4
c-myc	Avian myelocytomatosis virus	8(q24)	t(8;14)(q24;q23)	BL	3.5.6
c-abl	Abelson murine leukemia virus	9(q34)	t(9;22)(q34;q11)	CML	7.8
c-ras ^{H1}[x]	Harvey murine sarcoma virus	11(p11-pter)	Del 11p13	Wilm's	9.10
c-ras ^{K2}	Kirsten murine sarcoma virus	12	+12	CLL	11
c-fes	Snyder-Thielen feline sarcoma virus	15(q24-q25)	t(15;17)(q22;q12)	APL	1.2.7
c-src	Rous sarcoma virus	20	20q-	MPD	12.
c-sis	Simian sarcoma virus	22(q11-q13)	t(9;22)(q34;q11)	CML	13.14.15.16

[x] The genes designated ras constitute a multigene family (Ellis et al.,1981). Note: very recently we found (Geurts van Kessel and Nusse, 1983c) that the c-rasH1 oncogene is not included in the Wilms's tumor associated deletion of chromosome 11.

[xx] See chapter 1 and Rowley (1983)

1. Dalla-Favera et al. (1982b)
2. Harper et al. (in press)
3. Neel et al. (1982)
4. Prakash et al. (1982)
5. Dalla-Favera et al. (1982)
6. Taub et al. (1982)
7. Heisterkamp et al. (1982)
8. De Kleim et al. (1982) (Paper V)
9. Mc Bride et al. (1982)
10. De Martinville et al. (1983)
11. O'Brien et al. (1983)
12. Sakaguchi et al. (in press)
13. Swan et al. (1982)
14. Dalla-Favera et al. (1982a)
15. Groffen et al. (in press) (Paper VI)
16. Young et al. (submitted) (Paper VII)

Role of BCR/ABL in CML and other leukemia

As mentioned, a fused transcript of *BCR* and c-*ABL* is produced invariably in the CML cells. The protein produced by this mRNA is highly promising of malignant transformation. The function of BCR/ABL protein was elucidated by analogy to other proteins of known function. The viral origin of the protein,v-abl, shows tyrosine kinase activity, believed to mediate the malignant transformation caused by A-MuLV (Abelson murine leukaemia virus) (Witte O. N. et al, 1980). Enzymatic assays show that altered c-ABL protein from K562 leukaemia cell line exhibits tyrosine kinase activity (Konopka J.B. et al, 1984), which suggests its involvement in malignant transformation that underlines the CML. This hypothesis is confirmed by results from animal models as mentioned before (Groffen J. et al. 1992).

Later research reveal different structures of fusion protein that resulted from variation in breakpoints on the chromosomes. In c-*ABL*, the breakpoint lies within an intron 1 of 250kb. In *BCR*, the breakpoint lies in *bcr*, which represents a region of 6kb between exon 11 and exon 13. Juxtaposition of different gene fragment leads to different fusion gene and hence different mRNAs and proteins. There are three types of protein that can be resulted,$P210^{BCR/ABL}$ is present in 95% of CML patient, while $P190^{BCR/ABL}$ observed to be present in part of AML (acute Myelogenous Leukaemia) patients and $P230^{BCR/ABL}$ present in CNL (chronic neutrophilic leukaemia), a rare type of CML (Van Etten R. A. 2001). Activated BCR/ABL shows involvement in various types of leukaemia, indicating its vital role in malignant transformation.

Novel Treatment

Aiming on the tyrosine kinase activity of BCR/ABL, novel therapeutic strategies are raised and tested, among which the most successful one is with STI571, a 2-phenylaminopyrimidine derivative that selectively inhibits BCR/ABL (Druker B.J. et al, 1996). In a phase I trial concerning STI571(later named imatinib), a broad response is obtained in 46 of 58 patients of either CML or Ph-positive ALL, both expressing BCR/ABL in neoplastic cells. Eight of 46 shows a complete hematologic response, reaching remission (Druker B.J. et al, 2001a). In another phase I trial of STI571, 29 of 54 patients in chronic phase of CML shows a cytogenetic response after treatment with STI571, 7 of which shows a complete cytogenetic response (Druker B.J. et al, 2001b). In both trials, STI571 appears to be a useful treatment against BCR/ABL-present leukaemia whereas being well tolerated with nausea, vomiting as major side effects, much milder compared to that of preceding interferon or chemotherapy treatment. The later wide application of imatinib dramatically increases the quality of CML patients.

Conclusion

Chronic Myelogenous Leukaemia was the first human cancer to be found related to a chromosome anomaly. This discovery altered the way scientists view cancer and inspired a series of novel experiments that established a causative relation between BCR/ABL gene and CML. The study of malignant transformation mediated by activation of ABL inspired novel treating strategy based on the molecular finding, some of which was highly selective against cancer cells and thus slowed down progression of CML with less adverse effects. It is of intensive interests, however, to improve treatment for other cancer caused by a translocation adopting a similar strategy in research.

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Peer review:

Suggested Mark:3 50-59%

Good aspects of this essay: The essay is concise and well structured. There is good use of well researched scientific studies and the data obtained from these is integrated well to exemplify the points made. The work shows a strong understanding of the topic. There is a good and consistent focus on translocation and how it relates to CML.

Poor aspects of this essay: Some statements are not referenced. There is no bibliography and although one is not sure of your word count, overall the essay seemed a little rushed. (That's very true) I 'm only giving you a 2:2 because I believe that with a little more attention to detail and

elaboration and evaluation of some points, this could be an excellent piece, so do not be discouraged.

How can this essay be improved: not sure what your word count I but I think the essay is a bit short. You could elaborate on some of your points and examples from the studies you quoted a little bit more. (Reviewer's recommendation adopted) The essay also lacks a conclusion. (Reviewer's recommendation adopted) Make sure you reference everything that you got from other sources and make sure your referencing is consistent. (Reviewer's recommendation adopted) I believe the statements made in the paragraph starting "Simple and complex translocations." Need referencing too. "Progress in the etiology of CML" either needs a full stop after it and an underline to make it a subheading or needs to be integrated into a paragraph. (Reviewer's recommendation adopted)

Response to peer review:

I have corrected the grammar mistakes spotted and added bibliography and conclusion. Honestly that was an incomplete draft and you are right about the word count. Thank you for your objective review on my essay and your cheer.