

V. Clinical Sciences

C. Immune System Related Malignancies and Cellular Disorders

1. B cell and plasma cell neoplasms

LANDMARK ARTICLE:

Miller RA, Maloney DG, Warnke R, Levy R.

Treatment of B-cell lymphoma with monoclonal anti-idiotypic antibody

N Engl J Med. 1982;306:517-22

2. T cell neoplasms

LANDMARK ARTICLE:

Poiesz BJ, Ruscetti FW, Gazdar AF, Bunn PA, Minna JD, Gallo RC.

Detection and isolation of type C retrovirus particles from fresh and cultured lymphocytes of a patient with cutaneous T-cell lymphoma.

Proc Natl Acad Sci 1980;77:7415.

Retrovirus particles with type C morphology were found in two T-cell lymphoblastoid cell lines, HUT 102 and CTCL-3, and in fresh peripheral blood lymphocytes obtained from a patient with a cutaneous T-cell lymphoma (mycosis fungoides). The cell lines continuously produce these viruses, which are collectively referred to as HTLV, strain CR(HTLVCR). Originally, the production of virus from HUT 102 cells required induction with 5-iodo-2'-deoxyuridine, but the cell line became a constitutive producer of virus at its 56th passage. Cell line CTCL-3 has been a constitutive producer of virus from its second passage in culture. Both mature and immature extracellular virus particles were seen in thin-section electron micrographs of fixed, pelleted cellular material; on occasion, typical type C budding virus particles were seen. No form of intracellular virus particle has been seen. Mature particles were 100-110 nm in diameter, consisted of an electron-dense core surrounded by an outer membrane separated by an electronlucent region, banded at a density of 1.16 g/ml on a continuous 25-65% sucrose gradient, and contained 70S RNA and a DNA polymerase activity typical of viral reverse transcriptase (RT; RNA-dependent DNA nucleotidyltransferase). Under certain conditions of assay, HTLVCR RT showed cation preference for Mg²⁺ over Mn²⁺, distinct from the characteristics of cellular DNA 317 polymerases purified from human lymphocytes and the RT from most type C viruses. Antibodies to cellular DNA polymerase γ and anti-bodies against RT purified from several animal retroviruses failed to detectably interact with HTLVCR RT under conditions that were positive for the respective homologous DNA polymerase, demonstrating a lack of close relationship of HTLVCR RT to cellular DNA polymerases γ or RT of these viruses. Six major proteins, with sizes of approximately 10,000, 13,000, 19,000, 24,000, 42,000, and 52,000 daltons, were apparent when doubly banded, disrupted HTLVCR particles were chromatographed on a NaDodSO₄/polyacrylamide gel. The number of these particle-associated proteins is consistent with the expected proteins of a retrovirus, but the sizes of some are distinct from those of most known retroviruses of the primate subgroups.

3. Mast cell dyscrasias

LANDMARK ARTICLE:

Schwartz LB, Metcalf DD, Miller JS, et al.

Tryptase levels as an indicator of mast-cell activation in systemic anaphylaxis and mastocytosis

N Engl J Med 1987 316:1622-1626

Better methods are needed to assess mast-cell activation in vivo and to distinguish the activation of mast cells from that of basophils. Tryptase, a neutral protease selectively concentrated in the secretory granules of

human mast cells (but not basophils), is released by mast cells together with histamine and serves as a marker of mast-cell activation. In 17 patients with systemic mastocytosis, concentrations of tryptase in plasma were linearly related to those of histamine (P less than 0.01). Eleven of the 17 patients had tryptase levels of 4 to 88 ng per milliliter, indicating ongoing mast-cell activation. In each of six patients who experienced corresponding anaphylactic reactions after penicillin, aspirin, or melon ingestion, a wasp sting, exercise, or antilymphocyte globulin injection, tryptase levels in serum ranged from 9 to 75 ng per milliliter, indicating mast-cell activation during each of these events. In contrast, serum tryptase levels were less than 5 ng per milliliter in all patients presenting with myocardial disease (n = 8, 6 with hypotension) or sepsis (n = 6, 3 with hypotension) and in the controls (n = 20). One patient had a myocardial infarction after anaphylaxis in response to a wasp sting and an elevated tryptase level of 25 ng per milliliter. Thus, the plasma or serum tryptase level is a diagnostic correlate of mast cell related events.

4. Eosinophilic disorders

LANDMARK PAPER:

Cools J. DeAngelo DJ. Gotlib J. Stover EH. Legare RD. Cortes J. Kutok J. Clark J. Galinsky I. Griffin JD. Cross NC. Tefferi A. Malone J. Alam R. Schrier SL. Schmid J. Rose M. Vandenberghe P. Verhoef G. Boogaerts M. Wlodarska I. Kantarjian H. Marynen P. Coutre SE. Stone R. Gilliland DG.

[A tyrosine kinase created by fusion of the PDGFRA and FIP1L1 genes as a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome](#)

ABSTRACT BACKGROUND: Idiopathic hypereosinophilic syndrome involves a prolonged state of eosinophilia associated with organ dysfunction. It is of unknown cause. Recent reports of responses to imatinib in patients with the syndrome suggested that an activated kinase such as ABL, platelet-derived growth factor receptor (PDGFR), or KIT, all of which are inhibited by imatinib, might be the cause. **METHODS:** We treated 11 patients with the hypereosinophilic syndrome with imatinib and identified the molecular basis for the response. **RESULTS:** Nine of the 11 patients treated with imatinib had responses lasting more than three months in which the eosinophil count returned to normal. One such patient had a complex chromosomal abnormality, leading to the identification of a fusion of the Fip1-like 1 (FIP1L1) gene to the PDGFRalpha (PDGFRA) gene generated by an interstitial deletion on chromosome 4q12. FIP1L1-PDGFRalpha is a constitutively activated tyrosine kinase that transforms hematopoietic cells and is inhibited by imatinib (50 percent inhibitory concentration, 3.2 nM). The FIP1L1-PDGFRalpha fusion gene was subsequently detected in 9 of 16 patients with the syndrome and in 5 of the 9 patients with responses to imatinib that lasted more than three months. Relapse in one patient correlated with the appearance of a T674I mutation in PDGFRA that confers resistance to imatinib. **CONCLUSIONS:** The hypereosinophilic syndrome may result from a novel fusion tyrosine kinase - FIP1L1-PDGFRalpha - that is a consequence of an interstitial chromosomal deletion. The acquisition of a T674I resistance mutation at the time of relapse demonstrates that FIP1L1-PDGFRalpha is the target of imatinib. Our data indicate that the deletion of genetic material may result in gain-of-function fusion proteins.

LANDMARK ARTICLE:

Schrezenmeier H, Thome SD, Tewald F, et al.

[Interleukin-5 is the predominant eosinophilopoietin produced by cloned T lymphocytes in hypereosinophilic syndrome.](#)

[Exp Hematol. 1993;21:358-65](#)

oned T lymphocytes (TLC) of the CD4+CD8- phenotype established from peripheral blood of a patient with idiopathic hypereosinophilic syndrome (HES) were found to release a lineage-specific eosinophilic colony-stimulating factor (Eo-CSF). The present study was undertaken to identify the lymphokine accounting for this Eo-CSF activity. Comparison of TLC-derived Eo-CSF with recombinant human

interleukin-5 (rhIL-5), recombinant human granulocytemacrophage colony-stimulating factor (rhGM-CSF) and recombinant human interleukin-3 (rhIL-3) by in vitro clonogenic assays revealed similar bioactivity of HES-derived Eo-CSF and IL-5. Neutralization studies using specific antibodies against IL-5, GM-CSF and IL-3 confirmed that IL-5 mainly accounts for the Eo-CSF activity in all 9 HES-derived TLC tested. Eosinophilic colony (CFU-Eo) formation supported by conditioned media of the TLC was significantly inhibited in all clones by addition of anti-IL-5 monoclonal antibody (MAB) to the conditioned media. Inhibition by anti-IL-5 MAB was specific and dose-dependent. In 2 of the 9 clones, anti-GM-CSF antibodies could partially neutralize the Eo-CSF activity in the conditioned media. In 4 clones, addition of a combination of anti-IL-5 MAB and anti-GM-CSF antiserum to the conditioned media reduced CFU-Eo formation significantly more than addition of anti-IL-5 MAB alone. In none of the TLC could a significant role for IL-3 in eosinophilic colony formation be shown. These results were confirmed at the mRNA level. Cytokine transcripts were detected by reverse transcription (RT) and subsequent polymerase chain reaction (PCR). Under the same experimental conditions, all HES-derived TLC, but only one third of tested TLC from healthy donors, expressed IL-5 mRNA 5 days after stimulation. In control TLC with inducible IL-5 mRNA expression, IL-5 transcripts were found for only 3 days after stimulation. In contrast, HES-derived TLC contained IL-5 mRNA at least until day 18 after restimulation. All HES clones expressed GM-CSF mRNA upon stimulation. Two HES-derived TLC were found to lack IL-3 mRNA even after stimulation. Whereas IL-5 was expressed abundantly in all HES clones, the intensity of PCR products for GM-CSF and IL-3 showed striking differences. Our in vitro results suggest that IL-5 produced by activated CD4+ T lymphocytes plays a crucial role in the induction of eosinophilia in HES. In addition, GM-CSF but not IL-3 seems to contribute partially to the increased eosinophil production in HES.

5. Cryopathies and amyloid

[LANDMARK ARTICLE:](#)

[Levo Y , Gorevic PD , Kassab HJ, et al](#)

[Association between hepatitis B virus and essential mixed cryoglobulinemia](#)

[N Engl J Med 1977;296:1501-1504](#)

In view of a high frequency of liver involvement in patients with essential mixed cryoglobulinemia, we looked for evidence for hepatitis B virus infection in 25 serum specimens and 19 cryoprecipitates obtained from 30 patients. Three of the 25 serum specimens contained Hbs Ag, and 12 had antibody. The frequency of positive results was increased to six and 11 of 19 respectively when cryoprecipitates were examined, and 14 of 19 (74 per cent) of the cryoprecipitates were positive for either HBs Ag or its antibody. Electron microscopy of four cryoprecipitates showed structures resembling the 20-nm and 27-nm spheres, tubules, as well as the Dane particles characteristic of hepatitis B virus infection. Since such infection appears to be involved in the pathogenesis of the syndrome, the term "essential mixed cryoglobulinemia" should be replaced by "mixed cryoglobulinemia secondary to hepatitis B virus" or perhaps to other viral infections.