EDITORIAL

Chemical Exposure, ras Oncogene Activation, and Acute Myeloid Leukemia

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Interest in the association between mutations in the ras family of oncogenes and acute myeloid leukemia (AML) began with the description of a point mutation in N-ras (also known as NRAS) in a patient with AML (*1*). Since then, clinical reports suggest that 15%-30% of patients with AML exhibit ras oncogene activation, making it the single most common genetic perturbation in AML (*2,3*). The vast majority of these mutations occur in N-ras. Occasionally, K-ras (also known as KRAS2) mutations are found. Mutations in H-ras (also known as HRAS) are very rarely demonstrated (*2,3*). The role of ras oncogene activation in AML patients remains unclear and can occur either early or late in the development of the disease (*2-4*). Mutation in ras oncogenes probably represents one of many genetic events that occur in leukemia. This mutation, however, could be especially important in the early stages of leukemia development, because it may cause chromosomal instability and increase the probability of other genetic alterations (*5,6*).

If ras mutations had no functional role in leukemia development, they would occur randomly and at similar frequencies in different leukemias. This situation is not the case. Although the incidence of these mutations in AML patients is 15%-30%, in patients with acute lymphocytic leukemia, it is lower—only 10%-18%. In patients with chronic myeloid leukemia, the incidence is less than 5%, and in those with chronic lymphocytic leukemia, it is 0% (*3*). The highest incidence of ras mutations occurs in patients with the myelodysplasia subtype of chronic myelomonocytic leukemia, where 68% of patients carry a mutation (*3*). Thus, such mutations may be particularly important in specific subcategories of the leukemias and less important or unimportant in others.

To clarify relationships between specific exposures and disease occurrence in an epidemiological sense, it is important to classify disease outcomes into subgroups that are as homogeneous as possible. In this manner, exposure associations confined to a specific subtype can be clearly identified. In this issue of the Journal, Taylor and his co-workers (*7*) argue that, since AML appears to be a heterogeneous disease at the molecular and cytogenetic levels, it is possible that certain environmental agents might be linked to specific molecular subtypes. Using ras mutation-positive (ras-positive) AML as a molecular subtype, they go on to show that this form of leukemia is strongly associated with employment in any of 32 a priori occupations reported to be associated with increased leukemia risk (*7*). Patients with ras-positive AML had a significantly higher frequency of working 5 or more years in an a priori high-risk occupation than did population-based control subjects (odds ratio [OR] = 5.9). Furthermore, ras-positive AML patients were more likely than control subjects to have had dermal exposure (OR = 4.5) or to have breathed chemical vapors on the job (OR = 3.0), associations which became stronger after exposure status was reclassified on the basis of use of protective equipment. Similar results were obtained when exposure patterns among ras-positive and ras mutation-negative (ras-negative) patients were compared.

Earlier studies (*8-11*) had shown a link between chemical exposures and cytogenetically characterized subtypes of AML, e.g., association of alkylating agents used in chemotherapy with aberrations in the –5/–5q and –7/–7q chromosomal regions; association of occupational exposure with these aberrations plus aberrations in t(8;21) and trisomy 8; and association of smoking with aberrations in +8 and inv(16). The study by Taylor et al. (*7*) is the first, however, to use mutations in a proto-oncogene, which lead to activation of the oncogene, to subclassify leukemia and relate the subtype of AML characterized by ras mutation activation with employment in an occupation associated with elevated leukemia occurrence and substantial chemical exposure. In an important paper in the *American Journal of Epidemiology* in 1989 (*12*), Taylor suggested that oncogene assays could become a powerful epidemiological tool for investigating tumor etiology. His group's article in this issue further advances that concept. It is interesting to note that the occupational associations observed in this study would not have been detected had ras-positive and ras-negative patients been analyzed as a single group. This observation suggests that the leukemogenic potential of some previously studied occupations and chemical exposures may have been underestimated. Moreover, ras mutations tend to be chemical specific (*13,14*); thus, a larger study of ras-positive leukemias may enable identification of associations between specific ras mutations and particular chemical exposures. Application of molecular genetics may, therefore, significantly enhance the potential for epidemiological studies to

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identify risk factor associations with higher sensitivity and specificity.

The ORs described in the study by Taylor et al. (*7*) are large and the study is, indeed, noteworthy and suggestive. The findings are, however, based on relatively small numbers of patients, and the exposure assessment is confined to job title and general types of exposure information derived from questionnaires. Since exposures among workers with the same job titles may be heterogeneous and no detailed information was obtained about the specific chemical exposures, the findings from this study need to be followed up in future studies with detailed, validated exposure assessment. For example, Siemiatycki et al. (*15*) have developed a particularly effective method of obtaining exposure data in case-control studies. Questionnaires are reviewed by chemists and engineers who determine pertinent detailed occupational exposure questions to be asked in a second interview and who make follow-up visits to selected places of employment. Another option is to analyze archived material obtained from cohorts of occupationally exposed workers with well-defined exposure. With larger numbers of leukemia cases characterized as ras positive or ras negative and with state-of-the-art exposure assessment, we hope that investigators will be able to find exposure-specific abnormalities of oncogene activation.

Finally, it should be noted that ras-positive AML is found with equal prevalence in children and adults (*16,17*). The pattern of ras mutation activation is also very similar—mainly G to A transitions (*16*). Obviously, occupational chemical exposures cannot directly account for ras mutations found in childhood AML and must only account for a portion of those found in adult AML. However, it is interesting to speculate that the ras mutations found in childhood AML and other leukemias may be due to chemical exposures either in utero or in early life or, perhaps, even to parental exposure to occupational chemicals. Parental exposure has been suggested as a source of increased risk of childhood leukemia (*18*).

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