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ASTRONOMY

The Pristine Universe

Glenn G. Kacprzak

The existence of everything around us today sometimes seems far removed from the thermonuclear reactions occurring in the interiors of stars and stellar supernovae. These processes are responsible for producing almost all elements heavier than helium and for dispersing these elements throughout the universe. On page 1245 of this issue, Fumagalli *et al.* (1) report two gaseous regions that consist of virtually pristine gas (no detected elements heavier than helium) at an epoch where none are expected to exist. These findings demonstrate the nonuniform dispersion of elements throughout the universe, with direct consequences on the formation epoch of first-generation stars.

Our current understanding of the formation of the universe originates roughly 13.7 billion years ago with the Big Bang (2). This energetic event created space, time, light, fundamental particles, and the forces of nature. Present models state that this explosion cre-

ated dark energy (amounting to 74% of mass equivalent of the entire universe), dark matter (22%), and baryonic or ordinary matter (4%) (2). In the first few minutes, when the temperature of the hot plasma cooled below $\sim 10^9$ K, the first building blocks of stars formed from the electrons, protons, and neutrons. This event, called Big Bang nucleosynthesis (BBN), produced only hydrogen, deuterium, helium, and trace amounts of lithium (3). No other elements formed at this time, implying a virtually metal-free or pristine universe (in astrophysics, elements more massive than helium are described as metals).

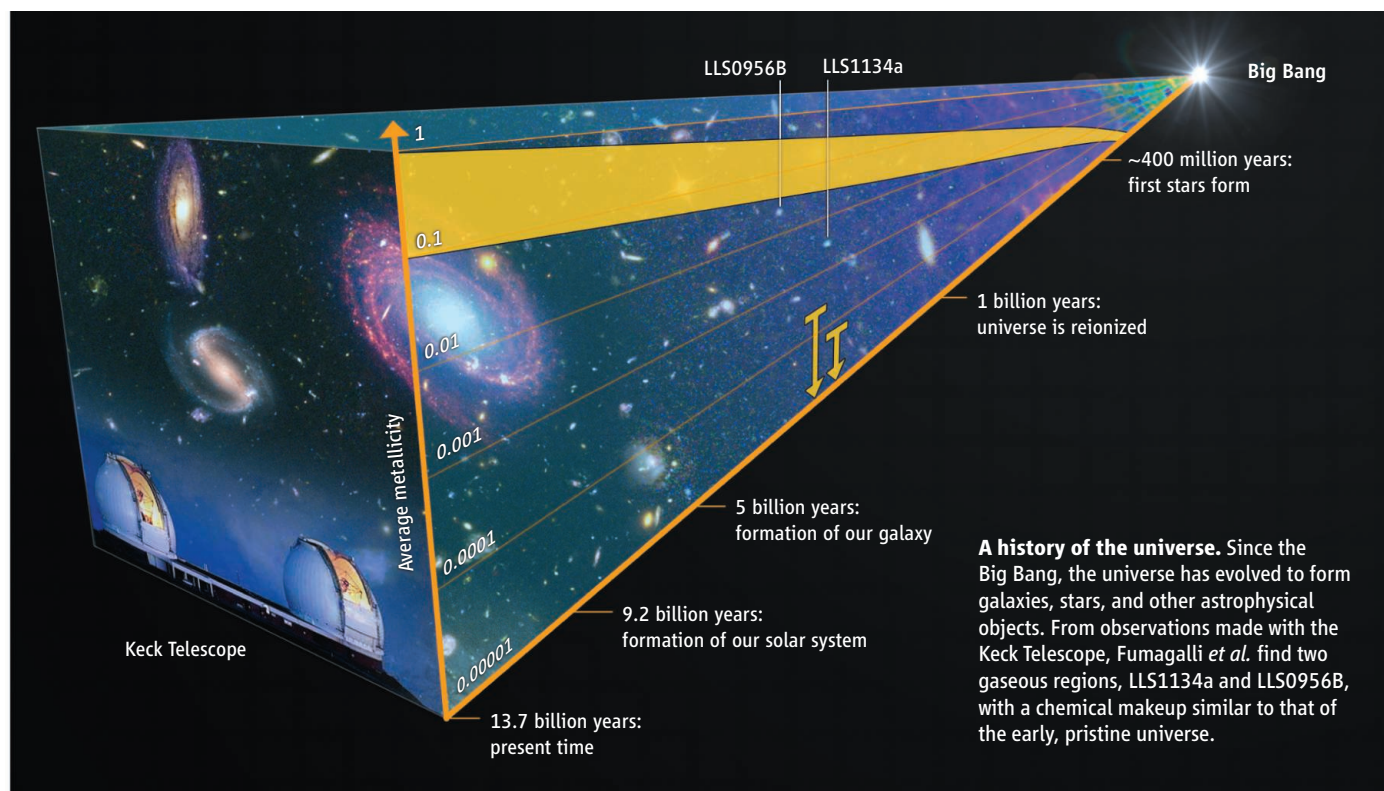
Around 400 million years later, as the universe expanded, it became cool enough for the first generation of stars, called Population III, to form from this primordial gas mixture. Although the existence of Population III, or metal-free stars, is based on cosmological models [see, for example, Hosokawa *et al.* (4) on page 1250 of this issue], their presence is proposed to account for the existence of the first heavy elements, which produced yields of 1/10,000th of the metallicity of our Sun (5). In the centers of these stars, the first

Observations reveal two gaseous regions with a composition close to that of the universe before the first stars were formed.

metals formed, and as they ended their lives as violent supernovae, creating additional heavy metals, they began to metal-enrich and ionize their surroundings. As new stars form out of the new enriched mixture (known as Populations II and I), they evolve and also disperse their additional metals, thus beginning the cycle of metal enrichment of the universe. To understand how efficiently or homogeneously metals are distributed, we need to measure metallicities of stars and gas as a function of time.

Metallicity measurements of individual stars are mostly limited to within our galaxy. However, there are a handful of stars in the halo of our galaxy that have roughly 1/10,000th of the metallicity of our Sun (6). These stars, although not first-generation Population III stars, are hypothesized to be remnants of an early epoch when the universe was mostly pristine. However, if it is the case that the distribution of metals is patchy, then these stars could have formed from pockets of pristine gas that remained unpolluted by metals at a later epoch. Obtaining metallicity measurements of stars is relatively easy

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compared with obtaining metallicity measurements of diffuse gas. Stars emit enormous amounts of light and can be seen with large telescopes, whereas faint diffuse gas barely emits any light and is therefore almost impossible to view.

A clever technique to probe the gas metallicity over the age of the universe is to use bright quasars as background light beacons, whose light passes through and is selectively absorbed by gas on its earthward journey. Imprinted on the quasar spectrum are the motions, chemical content, ionization balance, density, and temperature of the gas. Decoding the absorption fingerprints—spectral lines—provides details that are otherwise unobtainable using any other method of observation.

Using this technique, the chemical evolution of the universe from the present time to 1.3 billion years after the Big Bang can be mapped out (7, 8) (see the figure). Many models have also predicted the metallicity evolution since the birth of the first stars (9–12). A large variance in the metallicity measurements and in the models indicates that the distribution of metals is indeed patchy and not homogeneous. However, there are no gaseous systems found to have zero metals and, in fact, no diffuse gas has been found to have a metallicity below a “floor” of 1/700th solar (8).

Fumagalli *et al.* have discovered two gaseous regions ~2 billion years after the Big Bang that have zero observable metals. Calculated metallicity upper limits show that the true value must be less than 1/6000th (LLS0956B) and 1/16,000th (LLS1134a) of the solar metallicity—at least three orders of magnitude lower than the mean metallicity of the universe at that epoch and certainly well below the metallicity floor. These gaseous regions consist of virtually pristine gas at an epoch where none is expected to exist. Their discovery shows that the universe is not well mixed, and although we do not expect to see Population III stars today, it is possible that they could form in these massive reservoirs of pristine gas.

The BBN and measurements of the cosmic microwave background constrain the primordial deuterium-to-hydrogen (D/H) abundance ratio. Deuterium can only be created in BBN conditions and is easily destroyed by rapidly combining into helium. Thus, it exists only because of the rapid expansion and cooling of the universe, cutting short its conversion into helium. Therefore, the deuterium abundance is very sensitive to the initial conditions of the universe. The region LLS1134a has a measured D/H ratio consistent with the primordial value, providing

additional evidence that the gas is pristine.

The results of Fumagalli *et al.* show that virtually pristine gas can exist at later times in the universe than is expected due to the inhomogeneous distribution of metals. These regions, LLS1134a and LLS0956B, are the first pockets of near-to-pristine gas ever discovered. Although these systems are likely quite rare, they do provide the fuel for future formation of nearly metal-free stars as seen around our galaxy, or even Population III stars, implying that these stars do not need to form at early epochs as predicted by current models. These new findings add an exciting twist on the possible formation epoch of metal-free stars.

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MEDICINE

Personalized Cancer Diagnostics

Christopher L. Corless

A pilot study marshals sequencing resources and broad expertise to analyze patients’ tumors in a cost-effective and clinically relevant time frame.

More than a decade into the age of molecularly targeted cancer therapeutics, most clinical laboratories, which are required to operate under standards established by the U.S. Food and Drug Administration called the Clinical Laboratory Improvement Amendments (CLIA), are still using a one gene–one test approach to molecular diagnostics. For example, such tests are routinely used to screen for mutations in the gene encoding the signaling protein KRAS in colorectal carcinomas, and in the gene encoding the epidermal growth factor receptor in non–small cell carcinomas of the lung. There is a growing need, however, for broader approaches that can identify more rare mutations (e.g., mutations in the *ERBB2* and *BRAF* genes in lung carcinomas) that could have an impact on clinical care. Several CLIA labs have introduced multiplexed screens that cover as many as several hundred mutations across dozens of cancer genes (1, 2). But even these approaches are limited to mutation “hot-spots” and, for technical reasons, necessarily favor oncogenes over tumor suppressors. Larger panels of genes based on next-generation sequencing will be introduced by a number of labs in the immediate future; even so, some are asking: Why not sequence the entire genome of each patient’s tumor?

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Whole-genome sequencing can be used to devise unique tests to detect the recurrence of an individual patient’s tumor (3). Sequencing the entire genome of a leukemia uncovered a cryptic fusion gene that prompted a major change in the clinical management of the patient (4). Roychowdhury *et al.* (5) have now taken the approach one step further, sequencing not only the whole genome, but also the whole exome (the coding regions of the genome) and the whole transcriptome (the transcribed RNAs) of individual tumors in an effort to identify all potentially important anomalies. They show that this “sequence everything” approach can be done in a cost-effective and timely manner, delivering the ultimate in personalized cancer diagnostics and further opening the door to the new era of clinical cancer genomics.

The approach of Roychowdhury *et al.* focuses on cancer patients with advanced disease and uses a consent process that includes upfront genetic counseling and the option to accept or decline information on incidental genetic findings. Fresh biopsies were collected for whole-genome sequencing of the tumor DNA (5× to 15× coverage), whole-exome sequencing of tumor and matched normal DNA (70× to 100×), and whole-transcriptome sequencing. This combination of approaches allows orthogonal confirmation of the findings. For example, of the four cases presented, one was a metastatic colorectal carcinoma in which both genomic