throughout development (see the figure). The next challenge is to understand how Fbw7/hCdc4/Ago is itself regulated and where it interacts with cyclin E in the cell. The issue of space is puzzling because cyclin E appears to have an exclusively nuclear location, whereas Fbw7/hCdc4/Ago has a transmembrane domain (*5*) suggesting that it is restricted to cellular membranes. By following the subcellular trafficking of cyclin E in living cells in real time, it should be possible to pinpoint where cyclin E and Fbw7/hCdc4/Ago interact. It will be important to work out the exact timing of cyclin E destruction: Is cyclin E continuously degraded, or is it only degraded after its mission has been completed?

Arguably, of greatest importance is the finding that mutations in Fbw7/hCdc4/Ago implicate this F-box protein in the pathogenesis of some forms of human breast and ovarian cancer (*6, 7*). Mutations prevent Fbw7/hCdc4/Ago from targeting cyclin E for ubiquitin-mediated degradation (see the figure), resulting in aberrantly elevated cyclin E, which promotes uncontrolled cell proliferation leading to cancer. Such loss-of-function mutations are a hallmark of a group of cancer-associated proteins termed tumor suppressors, and Fbw7/hCdc4/Ago qualifies for membership in this group. Interestingly, the cyclin E gene itself is overexpressed in many types of tumors (*9*) and belongs to the other major group of cancer-associated genes, the proto-oncogenes, which contribute to tumor formation through their excessive activity. Thus, there is a dark side to the interplay between cyclin E and Fbw7/hCdc4/Ago, as both are encoded by "dormant" cancer genes.

The cancer defects associated with Fbw7/hCdc4/Ago mutations shed new light on the mysterious finding that certain tumors including some breast tumors have elevated cyclin E protein in the absence of increased cyclin E gene amplification or mRNA production. In addition, the tumor suppressor protein pRb guards the transcription of cyclin E, and another tumor suppressor, the inhibitor p27, blocks cyclin E–CDK2 activity (see the figure) (*10, 11*). Collectively, aberrant forms of these proteins share the ability to promote overactivity of cyclin E–CDK2, and thus may have similar consequences: the deregulated growth of cells leading to cancer. Pinpointing precise defects within this delicate molecular machinery will help in the design of improved cancer therapeutics. It is encouraging that both inhibitors of cyclin E–CDK2 activity and modulators of ubiquitin-dependent proteolysis are among the emerging drugs being considered for cancer therapy.

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PERSPECTIVES: SURFACE SCIENCE

How Minerals React with Water

Gordon E. Brown Jr.

The interaction of aqueous solutions with mineral surfaces is one of the most important chemical reactions occurring in nature. Such reactions play a major role in dissolution, precipitation, and sorption processes (*1–3*), affecting the composition and quality of natural waters, the formation of soils, the removal of CO_2 from the atmosphere, the uptake and release of plant nutrients, the mobility of heavy metal contaminants, and the global cycling of chemical elements. They may also be responsible for the sequestration of water on Mars (*4*) and the formation of prebiotic molecules early in Earth's history (*5*). Interfacial reactions between solid surfaces and aqueous solution are also important in the preparation and performance of metal-on-metal oxide catalysts, metal corrosion and surface passivation, the cleaning of semiconductor surfaces, chemical sensing, and water treatment.

In addition to the presence of water and atmospheric gases, natural mineral surfaces are often coated with thin layers of precipitates, such as iron or manganese oxides, organic matter, and microbial biofilms (see the figure). This level of complexity is difficult to study at the atomic scale under reactive conditions. Nonetheless, rapid progress is being made because of the recent development of in situ surface-sensitive experimental methods, such as scanning probe microscopy (STM) (*1*), and x-ray spectroscopy (*1*) and scattering (*6*) methods that use extremely intense light from synchrotron radiation sources. Furthermore, computational studies (*7–9*) are beginning to provide realistic models of solid–aqueous solution interface reactions and structures that are consistent with experimental results.

Relatively simple mineral surfaces, such as periclase (MgO) (100) or corundum (α-Al_2O_3) (0001), are amenable to x-ray spectroscopic and scattering studies and high-level theoretical simulations. Synchrotron-based photoemission studies (*10, 11*) have shown that when water vapor first reacts with clean periclase or corundum surfaces, water molecules dissociate and react with a small concentration of defect sites at very low vapor pressures. Above a threshold pressure, water reacts with terrace sites, resulting in extensive surface hydroxylation. Recent theoretical simulations (*7–9*) are consistent with this interpretation.

The surface structure derived from these simulations is consistent with the structure of the hydrated α-Al_2O_3 (0001) surface recently determined with synchrotron-based crystal truncation rod diffraction (*12*). Heretofore, many surface and colloid chemists and geochemists assumed that hydrated mineral surfaces—particularly those of insulating materials such as corundum, which cannot be studied by STM—are adequately described as simple terminations of the bulk crystal structures. Eng *et al.* (*12*) showed that the upper atomic layers in the hydrated corundum surface are relaxed substantially relative to the bulk structure and the clean surface (*6*) and that the hydrated surface is oxygen- rather than Al-terminated, with each oxygen bonded to two Al atoms in the layer below.

This observation helps to explain the difference in reactivity between the clean and the hydrated alumina surface. The surface Al sites on the clean surface are strong Lewis acids. After hydroxylation, all surface sites are weak Lewis bases with lower reactivity to water but enhanced reactivity toward metals. This change may also help to explain the enhanced wettability of the hydrated alumina surface toward metals such as copper (*13*), which may alter the activity of alumina-supported Cu catalysts.

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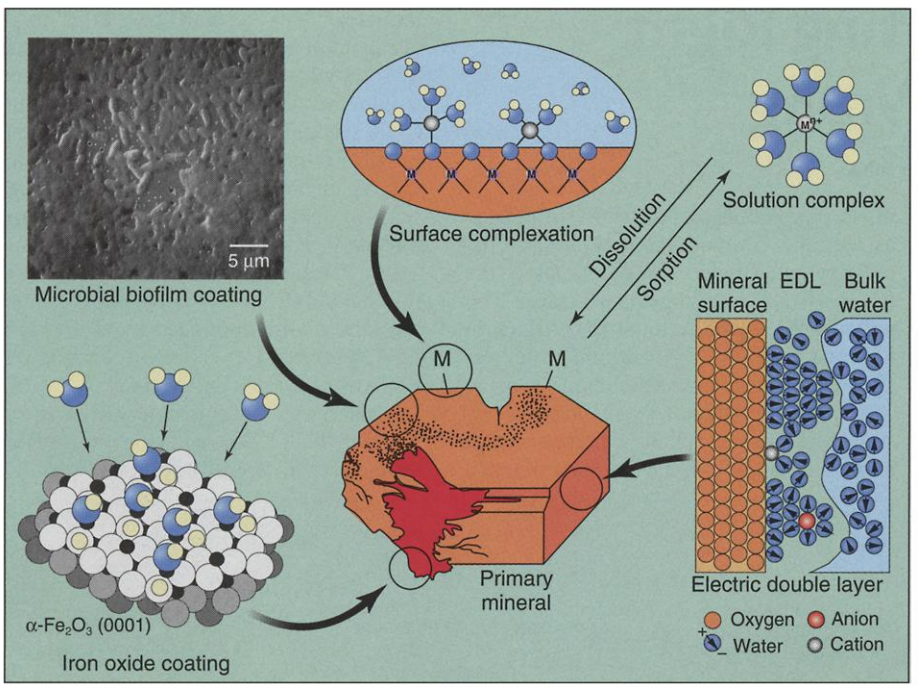
The surface structures of other hydrated minerals, including calcite (*14*), barite (*15*), and orthoclase (*16*) surfaces, have also been determined recently with high-resolution x-ray reflectivity measurements at synchrotron x-ray sources. For example, Fenter *et al.* (*14*) showed that the surface structure of calcite does not vary over a broad pH range, other than in the degree of protonation, contradicting earlier conclusions about calcite surface species based on surface complexation modeling (*17*).

on the transformation of redox-sensitive pollutant species, such as the reduction of selenate to elemental Se (*19*), on mineral surfaces. The finding that surface precipitation is an important process for sequestering certain heavy metal pollutants in soils (*20*) is particularly important for pollutant transport modeling.

Even more elusive than the mineral surface is the region adjacent to the surface that extends into the aqueous solution. This interfacial region is often described qualitatively with a family of electrical double layer (EDL) theories (*21*) (see the figure). EDL models describe the surface charge of the solid, the decay of the electrical potential away from the surface, and the concentration and distribution of cations and anions in both the compact and diffuse layers needed to neutralize the surface charge as a function of pH and ion concentration. Variations of EDL theory (*22*, *23*) are widely used in predictive models of sorption or surface complexation and the behavior of colloids.



A complex interface. This mineral–aqueous solution interface shows microbial biofilm and iron oxide coatings and some of the molecular-scale processes occurring at this interface, including interaction with water, sorption or surface complexation of aqueous metal ions, and dissolution. Also shown is a model of the EDL.

The next increase in experimental complexity is to react mineral surfaces with electrolyte solutions containing low concentrations of ions such as CrO_4^{2-}, AsO_3^{3-}, SeO_4^{2-}, Co^{2+}, Ni^{2+}, Pb^{2+}, and UO_2^{2+}, which are important soil and groundwater pollutants, and study the reaction products with spectroscopic methods. Here, synchrotron-based x-ray absorption fine structure (XAFS) spectroscopy is particularly useful because it is element-specific and can determine the molecular-scale speciation of reaction products at solid-water interfaces in situ, even at the low concentrations (parts per million) typical of heavy metal pollutants in soils. Such studies provide accurate descriptions of the structures and compositions of surface reaction products (*18*). Performed in real time, they also provide unique structural and kinetic information

Recent synchrotron x-ray standing wave (XSW) measurements (*24*) provide the first direct view of the EDL at the rutile (TiO_2)–aqueous solution interface. The study shows that EDL theory is generally correct for the rutile-water system. In addition, synchrotron x-ray reflectivity measurements (*25*) have provided the first nanometer-scale view of water structure at the muscovite (001)–water interface, with clear evidence that water is ordered in the interfacial region and has density oscillations.

Natural mineral surfaces are often coated with microbial biofilms. In a recent study, Templeton *et al.* address this added complexity (*26*) by using synchrotron XSW and reflectivity measurements to locate Pb^{2+} ions in the interface region of single crystals of α-Al_2O_3 and α-Fe_2O_3 surfaces coated by *Berkholderia cepacia* biofilms and the polysaccharide that they exude. The biofilm was expected to block reactive surface sites, resulting in lowered surface reactivity and increased bonding of Pb^{2+} to the bacterial surfaces or the polysaccharide. However, for low Pb^{2+} concentrations, lead was found to bond preferentially to the mineral surface. Only at higher Pb^{2+} concentrations, at which reactive surface sites are saturated, did lead bond to the biofilm.

The ability to probe complex mineral–aqueous solution interfaces on a subnanometer scale has led to detailed insights into how water reacts with mineral surfaces, how heavy metal ions and organic contaminants sorb on and desorb from mineral surfaces, the mechanisms by which mineral surfaces dissolve (*27*) and grow (*28*), and the structure and composition of the EDL at mineral-water interfaces, including those coated by organic matter or biofilms.

What is not yet known with much certainty are the structure and properties of water at such interfaces. There is experimental evidence that the dielectric constant of water near solid interfaces is an order of magnitude lower than that of bulk water at room temperature. This affects the ability of water molecules to reorient and should influence chemical reactions near interfaces.

Accurate knowledge of the structure and properties of interfacial water is essential for modeling the interaction of water and solute species with rocks, sediments, soils, building materials, and natural organic matter in nanometer-scale micropores, where the structure and properties of water are likely to be strongly influenced by surfaces. Also ripe for further investigation is the nature of defect sites on mineral surfaces in contact with aqueous solutions, including their role in dissolution and sorption reactions, and the mechanisms by which microbial organisms react with mineral surfaces.

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PERSPECTIVES: PROTEIN SYNTHESIS

Discriminating Right from Wrong

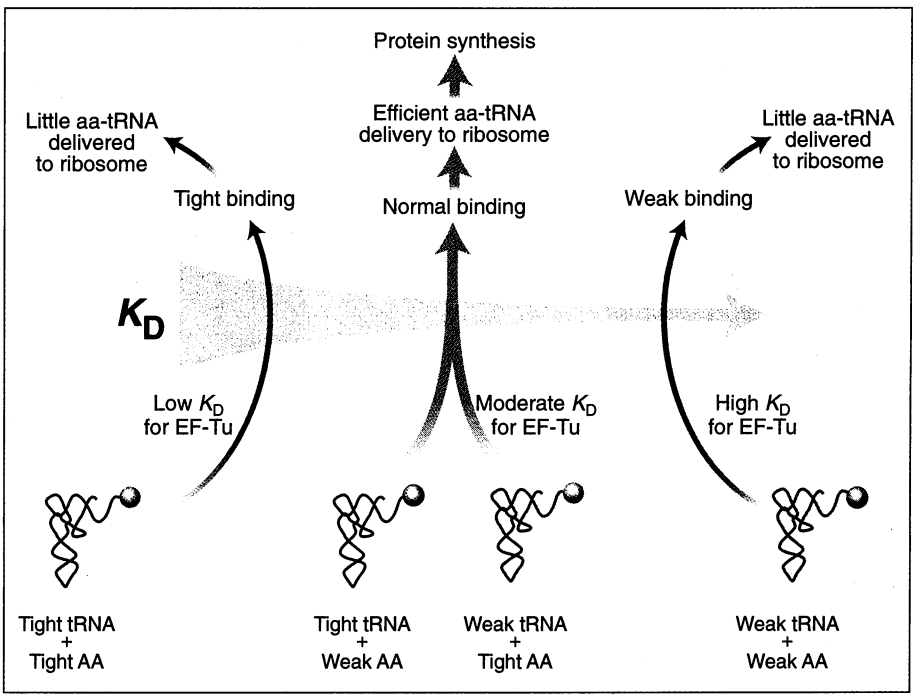
Michael Ibba

Ribosomes are the protein synthesis factories of the cell that translate the codons of mRNA into the corresponding polypeptide sequence. After initiation, protein synthesis proceeds by delivery of aminoacyltransfer RNAs (aa-tRNAs), each carrying the correct amino acid, to the ribosome's A-site. The delivery vehicle is a ubiquitous protein called elongation factor Tu (EF-Tu, also known as EF-1a), which is thought to be a nonspecific carrier as it binds to all 20 of the canonical aa-tRNAs. Although numerous quality-control checkpoints exist within the translation machinery, EF-Tu is not believed to be among them. This view is set to change with the work of LaRiviere *et al.* (*1*) appearing on page 165 of this issue. These investigators show that EF-Tu directly contributes to the accuracy of protein synthesis by binding to aa-tRNAs over a remarkably wide range of affinities.

Enhanced online at www.sciencemag.org/cgi/content/full/294/5540/70

Protein synthesis is a highly accurate process: Usually only 1 in every 10,000 codons in mRNA is decoded incorrectly (*2*). The accuracy of protein synthesis is believed to depend principally on the fidelity of both aa-tRNA synthesis and the interaction between mRNA codons and their tRNA anticodons (*3*). In addition, other components of the translation machinery may contribute to quality control in particular cases. For example, some organisms synthesize Asn-tRNA^{Asn} and Gln-tRNA^{Gln} through the mischarged intermediates Asp-tRNA^{Asn} and Glu-tRNA^{Gln}. These intermediates do not lead to the misinterpretation of Asn and Gln codons as Asp and Glu because they are specifically rejected by EF-Tu (*4*, *5*), as is the rare aa-tRNA carrying the so-called 21st amino acid selenocysteine (*6*). Although the structure of EF-Tu bound to an aa-tRNA indicates how specificity can be achieved for elongator versus initiator aa-tRNAs (*7*), the means by which particular elongator aa-tRNAs may be discriminated before delivery to the ribosomal A-site is less clear. This led LaRiviere *et al.* to investigate in more detail the affinity of EF-Tu for a wide variety of aa-tRNA species.

One of the challenges in studying substrate recognition by EF-Tu is the synthesis of a sufficiently wide variety of aa-tRNAs encompassing both tRNAs charged with the correct amino acids and those mischarged with the wrong amino acids. The difficulty lies in the generation of mischarged tRNAs, whose cellular synthesis is normally minimized by the intrinsic quality control exerted by aminoacyl–tRNA synthetases. LaRiviere *et al.* exploited existing knowledge about tRNA recognition by both EF-Tu and aminoacyl–tRNA synthetases to carefully introduce a number



Binding weakness to strength. Thermodynamic compensation during binding and discrimination of aminoacyl tRNAs (aa-tRNAs) by elongation factor Tu (EF-Tu). The functional groups comprising aa-tRNA, the aminoacyl (AA) and tRNA moieties, are recognized individually when they bind to EF-Tu. An aa-tRNA that contains two tightly binding moieties (red) has a low dissociation constant (K_D) for EF-Tu, whereas one that has two weakly binding moieties (blue) has a high K_D for EF-Tu. In both cases, the affinity for EF-Tu, whether high or low, is beyond the range for optimal delivery of the aa-tRNA to the ribosomal A-site. Combinations of a tight and a weak binding moiety in an aa-tRNA optimize the affinity of that aa-tRNA for EF-Tu, resulting in its subsequent delivery to the ribosome.

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