

CHEMISTRY

Nanosilver Revisited Downstream

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Hundreds of consumer products are on the market that contain metallic silver nanoparticles. Given the potential toxicity of silver, these engineered nanoparticles are currently under intense scrutiny by environmental and occupational scientists (1) and regulators (2). The reason for this interest is that the physical and chemical properties of particles in the nanorange (from about 1 to 100 nm) can be different from larger particles or dissolved compounds, and it is not yet clear whether these different properties also require a new and more rigorous human and environmental risk assessment compared with their larger counterparts. In a recent article, Kim *et al.* (3) reported the discovery and identification of silver sulfide (Ag_2S) nanoparticles in sewage sludge. This finding provides some insight into the fate of silver that had been introduced in various forms into the environment.

Kim *et al.* found that silver is present in sewage sludge as nanoparticles of the α phase of silver sulfide ($\alpha\text{-Ag}_2\text{S}$), a phase found in nature as the mineral acanthite. Most of the silver that enters a wastewater treatment plant is removed during treatment, and it has been recognized that sulfide plays an important

role in the removal of silver (4). Silver enters wastewater from a variety of sources, both industrial (e.g., photographic and electronic industries) and from consumer products. Textiles containing nanosilver release silver into the wash water as the dissolved ions and as coarse particles, as well as in nanoparticle form (5, 6). Silver may also be discharged into wastewater as silver chloride precipitates (7).

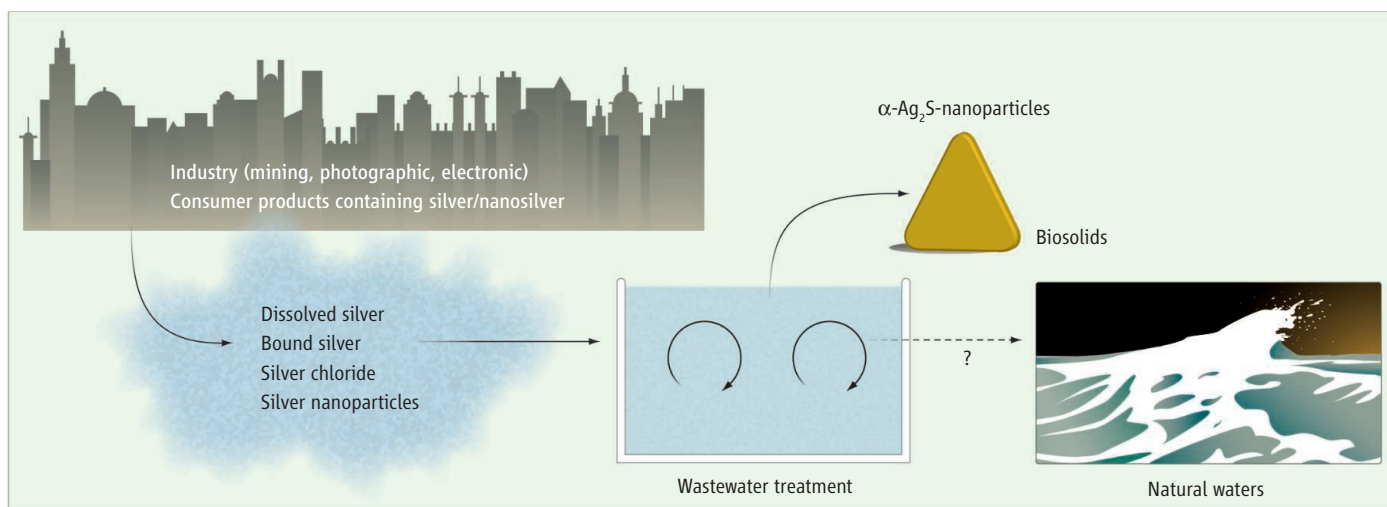
Initial studies showed that silver nanoparticles are efficiently removed from wastewater (more than 90%) and thus accumulate in the sludge (8). A recent study modeled concentrations of nanosilver from engineered products entering the environment based on the life cycles of these products and predicted that silver nanoparticles could be expected at concentrations of tens of nanograms per liter in natural waters (9). Kim *et al.* did not investigate the discharged treated water, so the form and concentration of silver present in the effluent water remains an open question. It can be expected that a certain fraction of silver will be bound to small flocs (aggregations of suspended particles) that are not retained during clarification and will contain $\alpha\text{-Ag}_2\text{S}$. Further investigations would be needed to determine whether surface modifications and coatings of engineered nanosilver make it more mobile and resistant to transformation reaction and produce less $\alpha\text{-Ag}_2\text{S}$ formation.

Wastewater treatment converts potentially toxic nanosilver particles into more benign silver sulfide nanoparticles.

A recent assessment of European silver flows into the environment (4) came to the conclusion that currently biocidal uses of silver (including silver nanoparticles, as well as silver in other forms, such as ionic silver) make up not more than 15% of the total silver flow into wastewater. If the situation is similar in the United States (where Kim *et al.* conducted their study), most of the Ag_2S nanoparticles in the biosolid sample that was investigated were formed from non-nanoparticulate silver. The results of Kim *et al.* suggest that dissolved silver, silver chloride precipitates, or metallic silver nanoparticles are transformed during wastewater treatment into Ag_2S nanoparticles that are retained in the sludge. Thus, even in the absence of introduced silver nanoparticles, wastewater treatment plants are efficient producers of silver nanoparticles, albeit of another mineralogical form than the metallic silver nanoparticles produced by industry.

If the formation of $\alpha\text{-Ag}_2\text{S}$ nanoparticles from all forms of silver constitutes the standard case for wastewater treatment plants, the environmental risk assessment of silver and nanosilver would be simplified greatly. Silver is one of the most toxic metals to microorganisms and is also quite harmful to many other ecologically relevant species (1), but the speciation of silver strongly affects its toxicity. Silver bound to sulfur or organic ligands

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Silver trails. Silver enters the environment from a variety of sources (industrial and consumer products) in different forms (as ions, nanoparticles, and coarser particles, and as compounds, such as silver chloride). The work of Kim *et al.* now

suggests that all the different forms of silver are transformed into the mineral $\alpha\text{-Ag}_2\text{S}$ during wastewater treatment. It remains open whether and in which form silver is present in the effluent.

is many orders of magnitude less toxic than the free silver ion (4, 10). α - Ag_2S is one of the most insoluble silver minerals known, whereas metallic silver nanoparticles are an efficient source of silver ions in natural waters (11). If the majority of the silver is present as α - Ag_2S in sludge or in the effluent from the treatment plant, then its toxicity cannot be evaluated using data obtained in studies with either dissolved silver or metallic silver nanoparticles. From an environmental point of view, the use

of nanosilver in consumer products would not be different from all other silver forms and would probably not constitute a problem for natural systems. It remains to be investigated, however, what the further fate of α - Ag_2S is in natural waters and whether it is transformed back to other silver forms.

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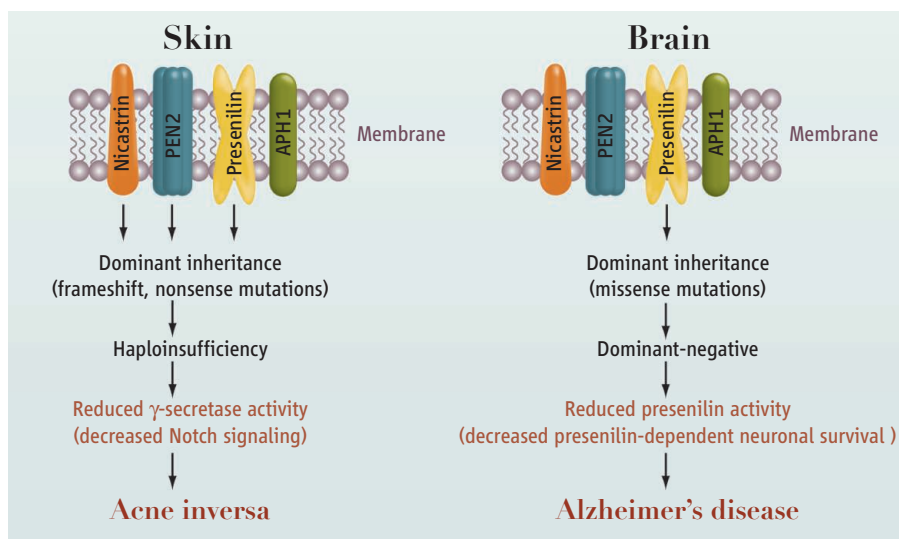
GENETICS

γ -Secretase and Human Disease

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The suspected culprit in Alzheimer's disease has been γ -secretase, an enzyme that cleaves type I transmembrane proteins. It processes amyloid precursor protein (APP), generating the β -amyloid ($\text{A}\beta$) peptides that give rise to the characteristic brain plaques of Alzheimer's disease patients. Presenilin is the presumptive catalytic subunit of γ -secretase, and mutations in the *PSEN1* and *PSEN2* genes that encode this subunit are the most common cause of familial Alzheimer's disease. On page 1065 of this issue, Wang *et al.* (1) report that mutations in *PSEN1* are also associated with a severe skin disorder, acne inversa. Mutations in genes encoding two other subunits of γ -secretase are also linked to this severe skin condition. The finding raises questions about the function of γ -secretase in human diseases, with implications for the development of therapeutics.

A key unresolved question is whether *PSEN* mutations cause familial Alzheimer's disease through loss of presenilin function and/or through increased production of longer $\text{A}\beta$ peptides (2, 3). *PSEN* mutations in familial Alzheimer's disease are almost exclusively missense, and the absence of nonsense or frameshift mutations argues against haploinsufficiency (only a single functional copy of a gene) and favors a disease mechanism based on gain of function by the mutant protein. However, the distribution of pathogenic mutations throughout the *PSEN* coding sequence is most compatible with a loss



Mutations and mechanisms. Dominant inactivating mutations in presenilin-1, nicastrin, and PEN2 cause acne inversa as a result of haploinsufficiency. Dominant missense mutations in presenilins-1 and -2 confer a loss of protein function and may cause Alzheimer's disease through a dominant-negative mechanism.

of protein function. Indeed, *PSEN* mutations that cause familial Alzheimer's disease impair the proteolytic activity of the mutant protein (2), and inactivation of presenilins in the adult mouse brain causes neurodegeneration (4), whereas $\text{A}\beta$ overproduction does not (5). In addition, γ -secretase inhibitors can mimic the effects of pathogenic *PSEN* mutations on APP processing, which suggests that overproduction of longer $\text{A}\beta$ is a manifestation of partial loss of presenilin function (2).

Wang *et al.* reveal that mutations in *PSEN1*, as well as in the *PSENEN* and *NCSTN* genes that encode the PEN2 and nicastrin subunits of γ -secretase, respectively, cause acne inversa. Six different mutations in these three genes were identified in six families with dominant transmission of a rare atypical form of acne inversa. Remarkably, all of the

The role of an enzyme in disease pathogenesis extends beyond Alzheimer's disease to a skin disorder.

mutations segregated with the disease with complete penetrance despite the genetic heterogeneity among the families. Because all of the mutations are predicted to inactivate protein function, haploinsufficiency of these genes appears to lead to acne inversa. This is consistent with mouse studies showing that γ -secretase deficiency produces follicular hyperkeratosis (6, 7), the initiating event in acne inversa. Similar disorders are observed in mice with skin-specific inactivation of the *Notch1* gene, which encodes another transmembrane protein cleaved by γ -secretase. This suggests that Notch1 is the enzyme's relevant substrate in acne inversa (8).

What do these findings from a disparate clinical disorder tell us about familial Alzheimer's disease? The major implication is that inactivating and missense mutations

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