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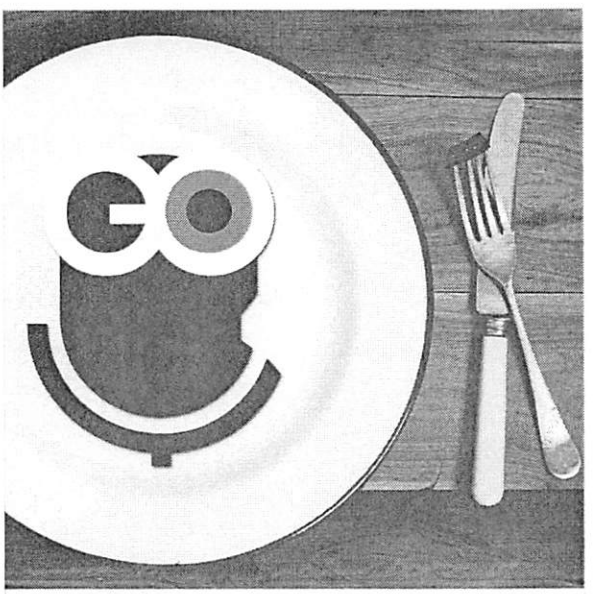

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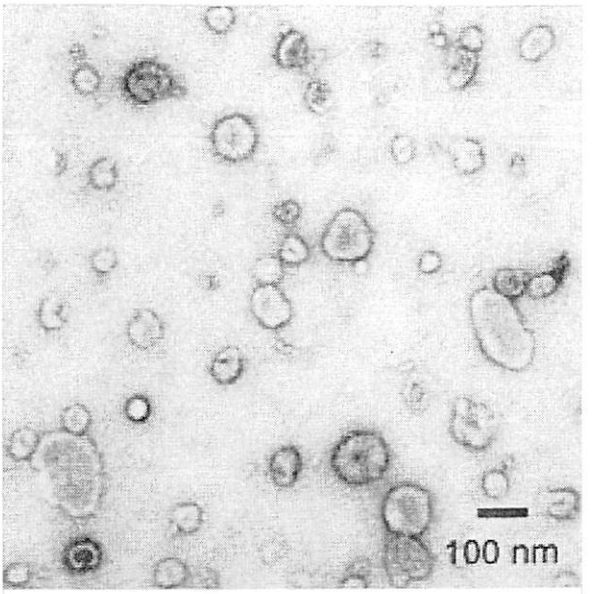

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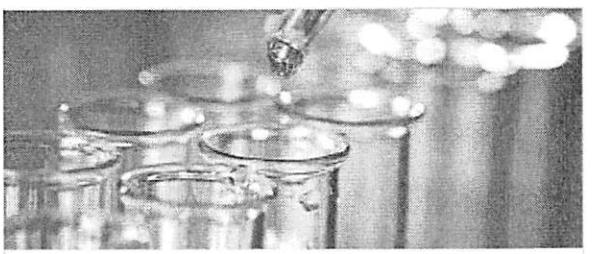

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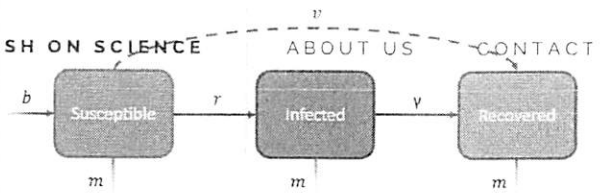

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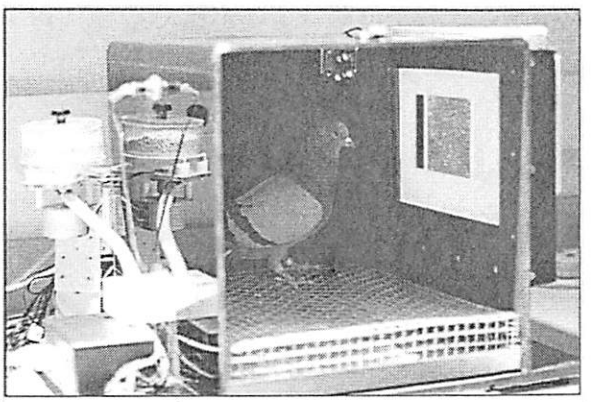

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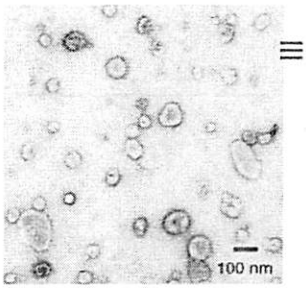

Transmission electron microscopy image of exosomes.

Scientists have known for decades that cells readily communicate with each other. To send signals close by, a communicative cell can nestle up to a neighbor that has the lock into which its key fits (a euphemism for ligand-receptor binding). To talk to other cells they aren't directly touching, cells can release substances such as hormones. These substances enter the circulatory system and eventually are sensed by other groups of cells that can respond to that specific signal. For many years, we thought those were the only two broad ways that cells could talk to each other: by directly touching or by releasing signaling molecules.

However, in the 1980s, a group of scientists first described tiny spheres, or vesicles, inside cells in a laboratory [1]. They noticed that these vesicles were eventually expelled into the cell's environment and therefore called them "exosomes." Since these vesicles originated in certain structures in the cell whose content was believed to be destined for degradation, the scientific community mistook this for a simple waste-disposal system of dying cells and everyone ignored them until the 1990s. It turns out this was a mistake; exosomes may be an incredibly efficient way to gather a huge amount of information about normal cells and disease states, and may even help us treat or cure certain conditions. The Birth of the Exosome

In the 90s, scientists noticed that exosomes were released in the environment by several types of living immune

cells and that they might be doing something useful [2]. The vesicles seemed to be made inside the cell, in membrane-bound compartments called endosomes. The endosome is responsible for recycling the cell's plasma membrane (different cell types recycle their whole membrane anywhere from once every 2 hours to once every half hour). This is done by pinching off a bit of the membrane, and then internalizing it into the inside of the cell as a spherical structure, the endosome. The endosome is a way for the cell to sort material derived from the plasma membrane and choose what it wants to deliver to the lysosome, the degradation center of the cell.

It turns out that the same process happens again inside some of these endosomes, when a part of the membrane is pinched off and internalized to make

little spherical vesicles [3] Eventually, this multi-vesicular endosome (MVE) travels to the cell's plasma membrane and opens up to fuse with it, at the same time pushing out its tiny vesicles into the extracellular space. These traveling membrane-bound sacs are called exosomes. (Prefixes to the rescue: endosomes internalize material from the membrane and sort it inside the cell; exosomes are externalized, and move material outside the cell). How Exosomes Affect Recipient Cells

Two decades later, our scientific knowledge and interest in exosomes has exploded. We've come to realize that exosomes are actually another route of intercellular communication. These vesicles are not only expelled by cells, but are then taken up by other cells, close and far alike, making them a kind of microscopic universal Amazon Prime. These tiny little packages hold

precious cargo such as proteins, fats, and RNA. Since exosomes are like tiny simplified versions of their donor cells, with an outer plasma membrane and a protected interior, their cargo is shielded from degradation. And when I say that exosomes are tiny, I mean it - about 40-120 nanometers in diameter. This means they are about 1000 times smaller than the average diameter of a human hair, which is 100 micrometers.

All cells seem to be able to secrete exosomes, and all cells seem to be able to receive them. Their cargo is a sampling of their donor cell's interior, but an imperfect one, since certain proteins or RNAs are often enriched. This tells us that at least some of the cargo is actively sorted and packed into exosomes, and not just there by statistical chance. However, how this packed cargo is chosen is still a mystery.

Besides delivering their cargo to recipient cells, exosomes can also send signals to cells through proteins that are embedded in their membranes. Just like neighboring cells can interact physically by ligand-receptor binding, exosomes with ligands displayed on their surface can bind to cells with the right receptor and stimulate signaling. This means that this traditionally short-distance form of communication can now be done long-range! On the flip side, exosomal cargo can also include receptor proteins, or the messenger RNAs that code for them. When exosomes meet a target cell, their plasma membrane fuses with the cell's membrane (a lot like what happens in the donor cell when exosomes are expelled). Receptors on the membrane of that exosome are now transferred to the membrane surface of the recipient cell, causing it

to "feel" signals through that receptor!

EXOSOMES IN HEALTH AND DISEASE

We now think that exosomes are an important way for healthy cells to communicate and function [4]. Some exosomes are used to excrete unnecessary proteins, just like the first observed vesicles were thought to do, but exosomes are also part of other normal processes like immune system function, responding to environmental changes, and tissue repair. For example, during pregnancy, placental cells release exosomes into the blood that carry inhibitory signals to protect the fetus from immune attack (since the fetus has different cells than the mother) [5]. Neural cells can excrete exosomes displaying neurotransmitter receptors to bind up all the neurotransmitters of

that type from a synapse (like a magnet would pull iron bits from its vicinity) in order to stop signaling [6]. In fact, we are finding that most organ systems use exosomes in their normal functions, begging the question: do exosomes play a role in disease?

It turns out exosomes may play a role in disease, but they could also be a means to treat disease. Exosomes have been shown to transfer pathogenic proteins such as viral particles [7] from infected cells to a healthy ones, or move amyloid deposits - the molecular cause of Alzheimer's - among neurons [8]. But not surprisingly, some of the most intensive research into exosomes and disease has been conducted in the context of cancer [9]. Not only have exosomes been observed to transfer oncoproteins [10] (proteins that promote cancer formation) into healthy cells, but they have been implicated in

a cancer's ability to escape immune detection and spread from a primary tumor to form new tumors at distant sites.

The immune system is supposed to kill all cells that cannot identify themselves as "self." All the healthy cells in our bodies display bits of themselves in surface proteins called MHC complexes, which are checked by immune cells passing by. If the immune cells recognize the bits displayed as part of the normal "self", the cells are safe. Cancer cells often have mutated, or "broken," proteins. If these broken proteins are displayed on MHC complexes, they are recognized as foreign, and immune killer cells will attack.

But we all know cancer is a smart disease, and it turns out it has lured exosomes into becoming its own malicious defense system. Tumor cells often excrete exosomes carrying

immune-inhibitory proteins, which signal to immune cells to stop attacking cancer cells. These "do-not-kill-me" signals then create a blanket of safety in the tumor environment, stopping the immune system from performing its protective functions [11]. Melanoma-secreted exosomes have even been observed preparing a cozy niche for incoming metastatic tumor cells, or cells that detach from the primary tumor, enter the blood system, and move to a distant site in the body to form another tumor called a metastasis. Exosomes are secreted from primary tumors and eventually come into contact with bone marrow cells, forcing them to excrete angiogenesis factors (molecules that encourage the growth of new blood vessels nearby) [12,13]. It's very important for metastatic cells to settle near blood vessels, which will allow them access to sugars, oxygen, and other

necessary nourishment to multiply and form a new tumor. These melanoma exosomes function as scouts who travel in front of spreading cancer cells, making sure their new environment will be optimal for growth.

Using Exosomes to Diagnose, Monitor and Heal

But I mentioned something about usefulness to heal disease, did I not? Exosomes could help us target and deliver drugs to certain cell types, and they might help us better predict, monitor, and understand diseases. Because exosomes are basically biological nanoparticles, we can isolate them from patients, stuff them with molecules of our choice, and inject them back into the same person to deliver crucial drugs [14] against many diseases [15]. They can even cross the blood-brain barrier, making them fabulous drug delivery agents for

neurodegenerative diseases like Alzheimer's or for brain cancers like glioblastoma [16]. Interestingly, the proteins that exosomes display on their surfaces may direct them to specific recipient cells; scientists haven't figured this out in detail, but when they do, we may be able to spare healthy cells the toxicity of some drugs, especially chemotherapeutics, targeting poisons specifically to infected, unhealthy, or cancerous cells.

Another useful tidbit about exosomes is that they are shed in every single bodily fluid tested thus far: saliva, urine, blood, semen, etc. And because exosomes are "samplings" of their donor cells, we can use what we find inside them to get a molecular "big picture" of the cell that secreted them - like what genes and proteins are highly represented. This is incredibly useful for cancer patients, for whom biopsies, which

usually are acquired by surgery, are the only way for doctors to gain molecular information about the patients' unique disease. After all, how many times can we really subject someone to surgery? So instead, doctors can isolate exosomes from urine, and use their cargo to assemble a blueprint of the kinds of cells, mutations, and irregularities found in the tumor [17]. This can provide not only diagnostic information, like how aggressive the cancer is or if it's likely to have spread already, but may also give us clues as to which drugs are most likely to work against that particular tumor. And, on top of that, since taking urine is painless to the patient and can be done often, we can even monitor a patient's disease over time, and response to treatment. This goes for many diseases, not just cancers.

The field of exosome study is just in its

beginning stage. Scientists are just now starting to characterize exosomes from different cell types, normal and diseased. We're only beginning to explore the possibility of using exosomes to deliver drugs in a targeted way. But most importantly, we might soon be able to diagnose, monitor, and cure some of the neurodegenerative and malignant diseases we have until now considered unstoppable, with a little help from our extremely tiny friends, the exosomes.

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