The signaling on the surface of cells is now referred to as the surfaceome.

Refer to the following to understand the MCFIP discovery of how these cell surface signaling molecules are created.

http://www.mcfip.net/upload/Cell%20Surface%20Signaling%20Molecule%20Formation%207-2017.pdf

Our model for the explicit explanation for endocytosis that transfers signaling from the surface into the cytoplasm is outlined in the following link.

http://www.mcfip.net/upload/Endocytosis%20Modeling%204-30-17.pdf

Putting a face on a cell surface

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On the cell surface, anchored in the cell membrane, a wide array of proteins perform functions, which are vital for the cell. These proteins, collectively known as the surfaceome, are a cell's antennae to the outside world, sending and receiving signals that enable it to communicate with other cells. They also serve as gate keepers for molecules, transporting materials into and out of the cell, and enable cells to attach themselves to other cells or structures.

The medical field has a keen interest in the surfaceome and uses it to treat diseases. Some two-thirds of known medications achieve their effect by slotting precisely into a specific surface protein and triggering a cellular signalling cascade.

Revamping the paradigm

Yet as practical and simple as that sounds, the current "one drug-one target" approach has a serious drawback: a given target surface protein can be found on many different cell types. Many drugs therefore attack not only the target cell type, but other cell types too. This is one reason why many drugs have unwanted side effects.

To find an alternative, researchers in Professor Bernd Wollscheid's group at the ETH Institute of Molecular Systems Biology and the Department of Health Sciences and Technology (D-HEST) are investigating the distribution and organisation of proteins on cell surfaces. Their goal is to take a fresh approach hoping to identify more suitable targets for drug intervention.

To date, the variety of the surfaceome in human cells has hardly been researched. In an initial step to remedy this, doctoral student Damaris Bausch-Fluck and bioinformatician Ulrich Goldmann, both members of Wollscheid's group, worked together to create an in silico inventory of these molecules. Their study was recently published in the journal *PNAS*.

The researchers made use of the benefits of machine learning in their work: First, they taught the computer to compile properties and features of surface proteins by feeding it with protein data collected in previous experiments. The computer turned presence of cell surface specific features into a score and then calculated a surfaceome score of the 20,000 or so proteins found in humans. Finally he predicted above which score a protein is likely to appear at the cell surface.

Predictions largely correct

In the end, the computer-generated inventory encompassed about 2,900 different proteins. In other words, out of all the proteins in a human cell, one in seven could appear on the cell surface. The newly developed algorithm achieved a high degree of accuracy in its predictions: a subsequent review of the experiment revealed that the computer was correct in more than 93 percent of cases.

In addition, the researchers were able to show that the number of surface proteins varies widely by cell type. Using publicly accessible data on cell lines, they were able to show that immune cells have only about 500 different surface proteins, whereas lung and brain cells have more than 1,000. But the cells that showed the greatest variety in surface proteins were primary stem cells, with about 1,800 different kinds. "Cell lines have a less complex surface proteome than cells that have just been removed from body tissue, since the interactions that cell lines undergo are less diverse," Wollscheid says. The ETH researchers have stored their findings in a public database.

Organisation and distribution are key

Identifying the incidence and diversity of proteins in the surfaceome does not automatically lead to new drugs, however. "Surface proteins are not evenly distributed, but are instead grouped like 'islands' in functional units. These units have varying combinations of proteins and thus varying functions," says Damaris Bausch-Fluck, who is lead author not only of the study mentioned above, but also of a review article for the journal Current Opinion in Chemical Biology. In the latter, she and her colleagues present different options for how the surfaceome might be organised at the nanoscale and how the "protein islands" can influence cell function and signalling.

The following analogy may help explain how surface proteins are arranged and their functions: if a protein were as large as a person, then the surface area of a cell would be three times the area of New York City's Central Park. A baseball field in the park would be one of these functional islands upon which proteins—the players—group themselves for a particular function—in this case, the baseball game. If the players leave the field, they lose their ability to function in this way.

Subsequent alterations change functions
Furthermore, each cell type creates surface proteins in different concentrations. Once they have been made, surface proteins can be altered, for example being "decorated" with sugar molecules or phosphates. As a result, they take on other functions that they would not otherwise perform without this molecular "garnish". This is why Wollscheid doesn't talk about proteins, but rather about proteoforms. The underlying structure may always be the same, but subsequent alterations to the original protein produce multiple different forms with various functions.

Islands as therapeutic targets
"In developing new drugs, it's crucial to know about functional units with multiple proteins and bear them in mind as potential targets," Wollscheid says. For example, instead of seeking out just one specific protein, antibody drugs could be designed to dock with several different targets simultaneously in order to neutralise a functional island. Since islands are much more specific to a given cell type, such as cancer cells, it is conceivable that this approach means diseases can be treated in a more targeted way and with fewer side effects.

"At present we're working to explore the many blank areas that remain on our maps of the surface of various cell types—almost like the pioneers of old who set off for unknown continents," Wollscheid explains.

Explore further: How to track and trace a protein: Nanosensors monitor intracellular deliveries
More information: Damaris Bausch-Fluck et al, The in silico human surfaceome, *Proceedings of the National Academy of Sciences* (2018). **DOI: 10.1073/pnas.1808790115**

Journal reference: Proceedings of the National Academy of Sciences