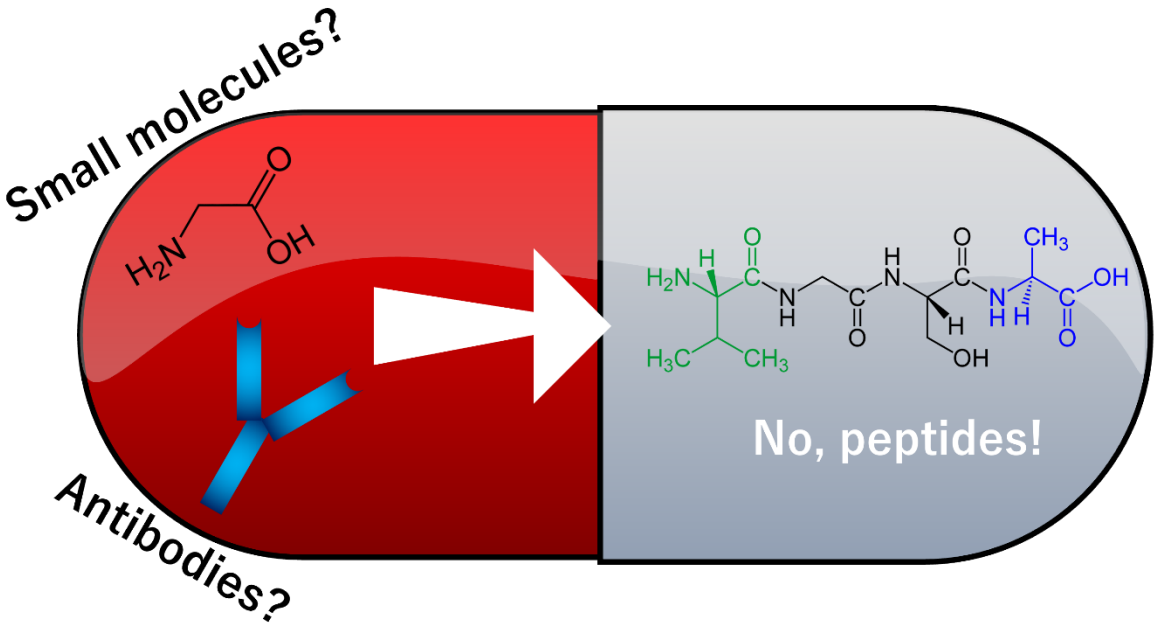

Beyond the Standard: Nonstandard Peptides at the Frontiers of Medicine

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If you are a high school student, you probably have heard about DNA, the ultimate blueprint of our body. Inside our body, we use information obtained from DNA to pick one from 20 amino acids and connect them one by one to create different molecules called peptides, and ultimately proteins, that work differently in our body. In this process, genetic code plays a key role. The main part of DNA is made of one of four different molecules, often symbolized as A, T, G, and C. The genetic code correlates different amino acids to different arrays of these molecules (e.g., “AUG” corresponds to amino acids called Methionine.) Inside our body, the molecule called mRNA “copies” the array, and correct amino acids are connected by the genetic code.

Because this genetic code system is such a sophisticated system, chemists have been trying to utilize this system to connect molecules, which can open a way to realize more efficient, highly selective (in other words, less chance of “unwanted” reactions) synthesis, or completely new chemical reactions. However, the system was “too sophisticated” to hack. Although there already were methods to realize this dream partially, they had some limitations in the peptides they could synthesize or the purity of the product. In other words, a method to connect amino acids with mRNA was not reported yet.

In 2007, a group of Prof. Suga and his colleague reported that they realized mRNA-directed reactions to connect molecules similar to amino acids[1]. To overcome the abovementioned problem, they used an approach to reprogram the genetic code. What they did is a bit tricky. When our body connects amino acids, molecules called tRNA carry amino acids to the point where amino acids are connected. The point here is that different tRNA carries different amino acids. This means genetic code is realized by tRNA. They modified tRNA to attach to different molecules from the original amino acids, which means reprograming genetic code; utilizing this reprogrammed genetic code, they synthesized a chain of molecules directed by mRNA. With this approach described above, they connected molecules called α-hydroxy acids to synthesize polyester, just like we connect amino acids in our body.

Their report itself may not be fascinating to many of us. It originally reported a new method to synthesize specific molecules. But it means not only reporting a new synthetic method to produce specific molecules. Prof. Suga‘s approach is not limited to the synthesis of their molecules: they can now control features of what they synthesize, like the length of the molecules and the order of unit (α-hydroxy acids at this time), by changing the mRNA, which is already helpful in chemical synthesis.

You may still have questions, though, like, “So what? What are you so happy about?” Indeed, the original research was just reporting a new way to synthesize new molecules efficiently, but it meant more than that: it opened a way to change the medical and pharmaceutical fields.

Countless drugs are around us, from cheap painkillers to drugs you've never heard of, with surprising costs. Generally speaking, cheaper drugs are made of simple molecules smaller than peptides, while expensive drugs have complicated structures, often more complex than peptides. Smaller molecule drugs are easy to absorb but often cause side effects. In our body, those molecules distinguish the targets that cause diseases, but small molecules are not smart enough to distinguish their targets correctly. These molecules have to judge potential targets they encounter by just one or a few parts of the molecular structures, and if the decision is wrong, we have to suffer from side effects. You may think: "You just have to make the molecules larger so they have more parts to judge the potential targets." That's true. One example is antibody-drug based on antibodies. Because antibodies are way larger than regular molecules (even larger than peptides), those antibody drugs are very selective to their target, as if different antibodies attack different viruses. Despite this strong advantage, these drugs come with high costs because we need bacteria or animal cells to synthesize antibody drugs. Another drawback is that they can't penetrate our cells, which often have the ultimate causes of diseases. You can see a dilemma here. If you use drugs made of smaller molecules, they are cheaper and often have several choices, but you suffer from side effects. If you use drugs without side effects, they are often costly, and in the worst case, there are no such drugs.
The synthesis based on mRNA offers a solution to this dilemma by making nonstandard peptides that can work as drugs in our bodies. What makes such peptides "nonstandard" is that the amino acids in those peptides differ from those in our bodies. Different amino acids give different functions to peptides, and peptides are often large enough to distinguish target molecules while small enough to make their way into cells. The only problem was synthesizing such peptides: you had to combine amino acids one by one, which is time-consuming and labor-intensive. Although mRNA-based synthesis was initially a fundamental chemistry, which may not be so exciting, it completely changed the situation. You just have to prepare a blueprint and leave all the other things to RNAs. Medicines made of "nonstandard"

peptides can have the merits of smaller molecules drugs and biopharmaceuticals while omitting their demerit, which became an alternative drug category[2].

As the requirement of the essay format, I declare that all part of the essay, including the text and the figure, was not generated by any generative AIs. Grammarly was used for checking spell and grammatical errors. Last but not least, I would like to thank both reviewers, Prof. Mark Vagins and Tatsuya Aonashi, for their comments based on objective viewpoints and many pieces of useful advice that helped me a lot to improve the first draft of this essay.

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