MPO-ANCA 関連血管炎の発症機構とガンマグロブリン開発

鈴 木 和 男
国立感染研・生物活性 (ksuzuki@nih.go.jp)

血管炎の発症は、myeloperoxidase (MPO) を抗原とする MPO-ANCA の血中レベルの上昇や、活性化好中球の関与がその発症に重要である。しかし、血管炎発症における好中球自己抗体や活性化好中球の役割は未だ解明されていない。急性進行性半月体形成性腎炎や川崎病の末梢好中球は、活性酸素産生能や MPO の放出能活性が上昇しており、末梢好中球は、活性化状態にあり、血管炎の発症に活性化好中球が深く関与していることを示唆している。一方、臨床マーカとして利用されている MPO-ANCA の抗体価の変動は、病初期の後は、疾患の病態と必ずしも連動しないことから、MPO-ANCA のクローンが病態に関与している可能性があるところから、エピトープによりクロナリティを調べた。その結果、MPO の H 鎖の N および C 末端に単独で反応するクローンが病態と関連があることが判明した。このクロナリティーに変化を及ぼすことが考えられる大量グロブリン治療免疫グロブリン治療(IVIg)の有効性が検討され、IVIg が有力な導入療法として期待されている。

Development of MPO-ANCA related vasculitis and its treatment with IVIG

Kazuo Suzuki
Laboratory of Biodefense, National Institute of Infectious Diseases (NIID-NIH)
Phone: +81-3-5285-1111 ext. 2329 Fax: +81-3-5285-1160 ksuzuki@nih.go.jp

Activated neutrophils may cause the development of vasculitis. Patients with MPO-ANCA related glomerulonepheritis (GN) and Kawasaki disease showed an increase of superoxide production and myeloperoxidase (MPO) release from neutrophils in peripheral blood, showing circulation of activated neutrophils. In addition, the antibodies against MPO and proteinase-3 (PR3) in neutrophil granules, anti-neutrophil cytoplasmic antibodies (ANCA), have been demonstrated to be associated with the development of vasculitis. Moreover, a higher percentage of MPO-ANCA in Japan than that in Europe has been reported. We have demonstrated that MPO is an antigen of MPO-ANCA using MPO-KO mice. However, it is not exactly related with disease activity in the late phase. Therefore, we have estimated the clonality of MPO-ANCA related with disease activity using epitope analysis, showing epitopes of MPO-ANCA reacting with N, and or C-terminals are related with the activity. The treatment with IVIg for vasculitis has been demonstrated in Japan, because of change in clonality of MPO-ANCA, probably.

ナノ粒子カンタムドットの感染症診断への応用

切替照雄(国立国際医療センター研究所感染・熱帯病研究部)
tkirikae@ri.imcj.go.jp

臨床検査の分野の中では、生化学部門は自動化と機械化が進んでいる。一方、感染症診断部門、とりわけ細菌検査部門は自動化がほとんど進んでいない。これは、この分野では熟練した技師による細菌の分離培養という作業が必須と考えられていたからである。これまでの診断法では、いったん原因微生物を分離すると、その微生物の性状を繰り返し検査できるという利点がある。しかし、必ずしも原因微生物を分離できるとは限らない、複合感染を見落としやすい、診断までに通常数日間はかかる、通常の診療ですべての感染症患者から原因微生物を分離培養する必要があるのか、など多くの問題点がある。このような点を考慮し、これまでの古典的な手法にかわる分離培養を必要としない感染症診断法の開発が望まれる。例えば、呼吸器症状を呈している患者の喀痰には複数の種類の病原体を含む微生物が存在する。それらすべてを迅速にできれば定量的に診断する方法が考えられる。また、薬剤耐性遺伝子の迅速診断法の開発も必須である。多色の蛍光を選択できるカンタムドットは、そのための有力な材料として使用できる。

Luminescent Quantum Dots for Multiplexed Diagnosis of Infectious Diseases

Teruo Kirikae, M.D., Ph.D.
Department of Tropical Medicine and Infectious Diseases, Research Institute
International Medical Center of Japan
tkirikae@ri.imcj.go.jp

Automation and mechanization is proceeding rapidly in the biochemical sections of clinical laboratories in hospitals and diagnostic centers. On the other hand, automation is not increasing in the microbiological sections, including bacteriological laboratories. The isolation of microorganisms by skilled microbiologists has been considered to be the first essential step to carry out microbiological diagnosis. Alternative diagnosis methods not having the isolation procedure should be developed. Samples such as sputum usually contain a number of species of microorganisms. In the developed methods, these organisms will be detected simultaneously, rapidly and quantitatively. Quantum dots with multi-luminescence will be a very useful tool for multiplexed diagnosis systems for infectious diseases.

ナノサイズ非ウイルスベクターを用いたDDSに関わる基礎検討

湯尾　明（国立国際医療センター研究所血液疾患研究部）
E-mail: yuoakira@ri.imcj.go.jp

本年度は、HVJ (Hemagglutinating Virus of Japan) エンベロープベクター（平均直径300nm）、高分子有機化合物ナノ担体という２つのナノキャリアーを中心として検討した。後者の担体に関しては、具体的には機能性リポソーム（平均直径100nm）を中心に検討した。これらを用いて、細胞内への標識分子の取り込みを検討した。標識方法に関しては、FITC、Alexa、などの従来から用いられてきた蛍光物質の他に、量子ドット (QD) そのものを用いた。FITC標識はオリゴヌクレオチドに、Alexa標識は蛋白に対して行った。標的細胞は、分担研究者が扱ってきたヒト血液細胞を中心に、一部の実験ではマウス血液細胞、付着系の細胞も用いた。HVJエンベロープベクターへの分子の封入は、低分子のオリゴ（FITCラベル）のみでなく、高分子の蛋白（Alexa標識）でも可能であった。さらに、QDの封入も可能であることを確認した。これらの標識分子は、QDも含めてHVJエンベロープベクターにより血液細胞内に高効率で導入できた。その導入状態はエンドゾームではなく細胞質に直接導入されていた。一方、環境応答性の機能性リポソームは、酸化還元状態に応じて膜透過性を発揮した。以上より、これらの２種類のベクターの有用性が示唆された。

Drug delivery system using nano-sized non-viral vector

Akira Yuo, MD, PhD, Department of Hematology, Research Institute,
International Medical Center of Japan, e-mail address: yuoakira@ri.imcj.go.jp

In the present study, we investigated the molecule-transducing capacity of HVJ (Hemagglutinating Virus of Japan) envelope vector (mean diameter: 300 nm) and novel stimuli-sensitive liposomes (mean diameter: 100 nm) as drug delivery system. FITC-labeled oligonucleotide and Alexa-labeled protein were efficiently enclosed into HVJ envelope vector, and this vector was able to efficiently transduce these enclosed molecules into human hematopoietic cell lines, which are known to be extremely resistant to gene transduction. In addition, we also found that quantum dot (QD) could be efficiently enclosed in HVJ envelope vector and efficiently transduced into the murine hematopoietic cell lines. HVJ envelope vector did this via direct transduction of enclosed molecules into the cytosol by non-endosome mechanism.

On the other hand, stimulus-sensitive arginine octamer-coated liposomes could be efficiently incorporated into cancer cells in response to reducing agent via the cleavage of disulfide-bond between the liposome and PEG.

These results strongly suggest potential usefulness of these non-viral nano-sized vectors in the drug delivery system.

量子ドットによるDDS

山本健二
国立国際医療センター (backen@ri.imcj.go.jp)

機能を持つ超分子の設計や製造またその運用を行うための考え方や、理論、またその実現のための手法をナノテクノロジーと呼ぶ。ここで化学物質（化学的要素）が複雑に関係しあい、全体としてまとまった機能を有するこのような粒子を超分子と呼ぶことにする。ナノテクノロジーは、対象とするもののサイズではなく超分子設計製造のための工学的技術である。ナノテクノロジーのひとつの重要な概念であり、また重要な技術はassembly と dis-assembly である。この技術について、次のセッションで紹介される。
人体内への薬剤伝達システム開発は、ナノテクノロジーの丁度良い対象となる。超分子ナノキャリアーは、製造され、薬物に結合され、体内に送り込まれ、標的臓器に薬物を伝達し、そこで薬物を放出する。薬剤の体内に於ける有効濃度維持時間は、半減期（薬物が体内で失活するか体内より外へ放出されるか）に依存する。相対的に長く保つには、高濃度のものを投与しなければならないが、それは望ましくない。投与すれば、ただちに有効濃度に達し、ある一定時間その濃度を維持し、減衰するときは次回投与のことを考えると一挙に減衰することが理想的である。
このようなことを実現するには、標的技術、センシング技術、放出技術等を開発する必要がある。ナノテクノロジーは、薬剤伝達システムの開発を発展させる道への鍵を握っていると考える。

Nano-technology is defined as the thoughts, theories and the methods in order to design the super molecule, to realize for the production and to utilize for the industry and the daily life. Here, we call the super molecule such as the particle consists the set of the chemical elements such as the any element has some complex relations with each other and, as a whole, has some comprehensive functions. The objects of the nano-technology are engineering technology to design and produce the super molecules and independent from their size. One of the important idea, view point and the technology for the nano-particle is the assembly and the dis-assembly which will be explained in the next session.

The drug delivery system in side the human body is a suitable field for the nano-technology to develop and collaborate. The carrier, the super molecule, should deliver the drug to the target organ and release the drug, which realize the pin-point drug therapy. One of the ideal drug to avoid the side effect would have such character that the drug concentration raises up to the efficient level immediately after the dose, holds the level for the constant period and comes back to the original level soon not to interfere with the following dose.

Targeting technology, sensing technology, and releasing technology will be necessary to realize the drug delivery system. The nano-technology have a key role to light up the pathway for the development of the Drug Delivery System completely.

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