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Review Article

COVID-19 遺伝子ワクチンによって誘発される終末分化組織における自己免疫性炎症反応

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抄録

SARS-CoV-2 の感染拡大を受けて、世界的なパンデミックが宣言された。COVID-19 ワクチンの無差別接種対象年齢群が拡大され、COVID-19 による重篤な合併症のリスクが最小限に抑えられた自然な免疫を有する個人も接種対象に含まれるようになった。免疫組織病理学的に得られた確かなエビデンスから、COVID-19 の遺伝子ワクチンは体内に広く分布し、注射部位から遠く離れた終末分化組織に影響を及ぼす可能性があることが実証されている。その中には心臓と脳が含まれており、これらの組織ではスパイクタンパク質が in situ で産生され、強い自己免疫学的炎症反応が惹起される可能性がある。非自己抗原を合成する全てのヒト細胞は必然的に免疫系の標的となるという事実のために、またヒトの体は厳密に区画化された系ではないため、どの組織が傷害されうるかを正確に決定するために正確な薬物動態および薬力学試験が必要である。したがって、本稿の目的は、COVID-19 に対する遺伝子ワクチンの生体内分布研究と年齢層別の合理的な被害-便益評価(harm-benefit assessment)が極めて重要であることに対して、科学界と規制当局の注意を喚起することである。

Keywords:

- COVID-19 genetic vaccines
- spike protein
- antigen presentation
- autoimmunity
- histopathology
- immunohistochemistry

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1.はじめに

SARS-CoV-2 の感染拡大を受けて、世界保健機関(World Health Organization:WHO)は世界的なパンデミック(世界的大流行)を宣言した。WHO の事務局長は 2023 年 5 月 5 日、COVID-19 の終息を公衆衛生上の緊急事態と宣言したが、この宣言は COVID-19 がもはや世界的な脅威ではなくなったことを意味するものではないと強調した[1]。このアウトブレイクに対する世界的な対応では、新しい遺伝子プラットフォームを用いた集団および無差別のワクチン接種に焦点が当てられた。市場への導入を促進するために緊急規制経路を発動したこと、および従来のワクチン(不活化または弱毒化ウイルスに基づく)に対する国民の固有の信頼によって、安全性と有効性に関する規制基準が引き下げられ、薬物や遺伝子治療に典型的な重要な薬力学試験、薬物動態試験、遺伝毒性試験を回避することが容易になった。そのため、ヒトにおける体内分布や生物学的持続性に関するデータが不足していたにもかかわらず数十億人がワクチン接種を受け、これらのデータは、数十億回の接種が行われた後、独立した研究または情報開示の自由(Freedom of Information disclosure)によって初めて得られたのである。遺伝子ワクチンが開発され、製造され、発売された速度は、より大きな利益のために世界各国の政府と協力して取り組んだ製薬業界の科学的手腕によって可能になった成果として一般に知られるようになったが、最近退職した Pfizer 社のワクチン研究開発部門の責任者であった Kathrin Jansen 博士の言葉を借りれば、「私たちはまだ飛行機を製造している間にそれを飛ばしてしまった」[2]。この「成果」には科学的な軽率さが関係しており、安全シグナル、ワクチンの否定的有効性および免疫回避のエビデンスが蓄積され続ける中で、この軽率さについては一層の精査が必要である。

このレビュー稿の背景にある理論的根拠は、COVID-19 に対する遺伝子ワクチンによって示されるオフターゲット分布という重大な問題に対処することであり、特に病理組織学的検査で得られた免疫組織化学所見に焦点を当てている。実際、最近の決定的な病理組織学的エビデンスから、SARS-CoV-2 に対する遺伝子ワクチンは注射部位を越えて分布することが示されており、重度の症候性損傷を受けやすい終末分化組織が関与している可能性がある。科学的エビデンスの合理的かつバイアスのない評価に基づき、利益相反がないことを宣言することで、ワクチン接種の安全性に関して深刻な懸念を表明する。特に、ワクチン接種による理論上のベネフィットがごくわずかである若年層および生来免疫のある人に対しては懸念を表明する。実際、前者は感染による致死率が非常に低く[3]、後者は自然免疫によって再感染や重症 COVID-19 に対する防御力がはるかに高い[4]。したがって、本稿の目的は、薬物動態学的および薬力学的研究ならびに年齢層別の合理的な被害-便益評価(harm-benefit assessment)が絶対的に必要であることに対して、科学界および規制当局の注意を喚起することである。

2.遺伝子ワクチンによる予防接種の機序

現在 COVID-19 の遺伝子ワクチンを推奨している多くの医師や科学者は、重要な免疫学的機序を見過ごし、自己免疫への影響を過小評価している可能性がある。暗にこの事実を危険と関連付けることはできないが、Pfizer 社でさえ、自社のワクチンがどのように作用するかを完全には理解していない。Senior Vice President for Vaccine Clinical R&D の Dr.William Gruber は、2022 年 6 月 15 日に開催された FDA の VRBPAC meeting で次のように述べた:「我々は、免疫応答を引き起こすという点でワクチンが作用する仕組みの性質を完全には理解していない」[5]。米国および EU で緊急使用が承認されている COVID-19 に対する遺伝子ワクチンは、mRNA(ヌクレオシド修飾)ワクチン(Pfizer/BioNTech 社および Moderna 社が製造)とアデノウイルスベクターワクチン(AstraZeneca 社および J&J/Janssen 社が製造)である[6,7]。これらのワクチンには、ヒト宿主細胞の機構を乗っ取って SARS-CoV-2 のスパイクタンパク質を合成し、それを免疫原として細胞表面に提示する遺伝情報が含まれている[8-10]。最も可能性が高いのは、スパイクタンパク質がリボソームによって翻訳されると、ゴルジ体で処理され、次の 2 つの方法で免疫系に提示されるということである:i)タンパク質全体(細胞膜上に提示され、B 細胞およびヘルパーT 細胞に認識される);および/または ii)タンパク質断片(主要組織適合抗原複合体 I[MHC I]に結合)[8,9,11]。

すべての有核細胞は膜上に MHC I を提示し、細胞内タンパク質のプロテアソームによる分解に由来する内因性抗原を CD8+T リンパ球に提示する[12-14]。この機序により、免疫系は全ての有核細胞のタンパク質合成活性をモニターすることができ、細胞が変異タンパク質、ウイルスタンパク質および/または非自己タンパク質を産生しているかどうかを同定することができる。MHC II は、全身で貪食された外因性抗原の断片を CD4+T リンパ球に提示するが、これはプロフェッショナル抗原提示細胞(professional antigen-presenting cell:APC)の細胞膜上に認められる[12,13]。免疫系がウイルス抗原を異物と認識すると、炎症反応が惹起され、抗原提示細胞が死滅する[12,13]。したがって、ヒト細胞にウイルスタンパク質の合成を誘導することによる遺伝子ワクチンは、本質的に T 細胞を介した自己免疫反応に依存して免疫応答を惹起する。

3.注射部位を越えた体内分布

ウイルスタンパク質を合成するすべての細胞が免疫系から脅威と認識されて死滅することを考慮すると[11]、遺伝子ワクチンの生体内分布を正確に把握することが極めて重要となる。正確な薬物動態および薬力学評価の必要性を指摘した著者もいる[11,15-18]。しかし、欧州医薬品庁(European Medicines Agency:EMA)の方針によれば、薬物動態試験は医薬品の安全性評価の基本的要素であるにもかかわらず、一般にワクチンには必須ではない[16]。したがって、これらのプラットフォームを「従来のワクチン」として分類することで、そのような評価を省略することが可能になった[16,19]。「従来のワクチン」であっても、免疫プロセス全体を通じて免疫系が自身の細胞を標的とするようになる可能性があることはよく知られている。しかし、遺伝子ワクチンと「従来のワクチン」との間には、いくつかの大きな違いがある。「従来のワクチン」については、生体内分布の評価は「一般的に必要」ではない。Polykretis と McCullough による書簡で述べられているように、不活化または不活化されたウイルスをベースとするワクチンでは、主にウイル

ス粒子を貪食してウイルス抗原を免疫系に提示する APC への提示が行われる[20]。このような細胞は、絶えず入れ替わりながら、生体内でこの特定の機能を果たしており、ある意味消耗品である。弱毒化ウイルスに基づくワクチンに関しては、毒性が弱く、免疫反応を引き起こすために少数のヒト細胞に感染する結果となる。

日本の医薬品医療機器総合機構(PMDA)が最初に公表し、Pfizer 社がラットを用いて実施し医薬品規制当局に提出された体内分布試験では、mRNA を含む脂質ナノ粒子(LNP)が注射部位を越えて主に肝臓、副腎、脾臓、卵巣およびその他の組織に蓄積することが示された[21]。前述の試験(試験番号 185350)で得られた知見に基づき、放射性標識した LNP およびルシフェラーゼ modRNA を注射したラットで検討した生体内分布に関して、2021 年 2 月 19 日付の EMA の Comirnaty(Pfizer/BioNTech)評価報告書の 47 ページには、「50μg の mRNA を 48 時間かけて筋肉内注射したときの血液、血漿および特定の組織への分布を測定した放射性標識データは、生物発光法よりも感度が高いと考えられ、生物発光法で観察されたものよりも広範な生体内分布パターンを示している。48 時間にわたり、注射部位からほとんどの組織への分布が認められ、大部分の組織で低レベルの放射能が認められた」[10]。したがって、EMA は、ラットでは注射部位を越えた分布が生じており、「ほとんどの(選択された)組織」に分布していることを認識していた。さらに、遺伝子ワクチンが血中で存続する可能性を示したエビデンスもある；Fertig らは、ワクチンに結合した合成 mRNA が注射後少なくとも 2 週間は血中にとどまることを発見した[22]。注目すべきことに、mRNA ワクチン接種後に心筋炎を発症した小児および若年成人から採取した血液検体で、血中に遊離スパイクタンパク質の存在が明らかにされた[23]。スパイクタンパク質を含むエクソソームは、ワクチン接種後 14 日目に血中で検出され、ブースター接種後に増加し、4 カ月間持続した[24]。化学動態と受動拡散の原理により、スパイクタンパク質をコードする遺伝物質を含む LNP が体循環中に長期間存在することで、遠く離れた組織にも到達することが可能になる。このことを裏付けるように、ワクチンの mRNA は母乳などの分泌物からも検出された[25]。さらに注目すべきことに、ワクチンの mRNA はリンパ節内で最長 8 週間残存する可能性があり[26]、当初 CDC が述べていた「数日」ではなくなった[27]。

4.エクソソームの役割

mRNA とスパイクタンパク質が全身に分布する機序の 1 つは、細胞外の小胞、特にエクソソームを介するものである。mRNA ワクチンのリリースに先立って実施された研究では、mRNA ナノ粒子に曝露されたヒト細胞から完全に無傷の mRNA 分子がエクソソーム中に放出され、それらのエクソソームがレシピエント細胞に取り込まれて、mRNA コードから完全に機能するタンパク質が合成される可能性があることが明らかにされた[28]。さらに in vitro 研究では、スパイクタンパク質をコードする mRNA ナノ粒子をヒト細胞に導入すると、スパイクタンパク質がエクソソームに放出され、それが脳内のミクログリアに取り込まれて炎症反応が惹起されることが実証された[29]。生体内分布に関する研究では、臓器の中では非常に高い濃度が脾臓で認められている。脾臓の胚中心にある免疫細胞は、抗体産生に不可欠なステップとしてエクソソームを放出する[30]。エクソソームは取り込まれた mRNA を分解から保護するとともに、血管やリンパ系を自由に移動するだけでなく、神経線維内を容易に移動する。脾臓から内臓神経および迷走神経に沿って移動し、心臓、肝臓、脳などの主要臓器に到達する可能性がある[31]。

遺伝物質のエクソソーム輸送は精巣などの生殖組織でも重要な役割を果たしており、精巣では精子を介した遺伝子導入(SMGT)として知られる現象が起こっていることが実証されている。これは、男性の体細胞由来の遺伝物質が、ゲノムに安定的に組み込まれなくても、低いコピー数で遺伝的モザイク様式で子孫に受け継がれる過程である[32-35]。最近、この現象はマウスの脳に直接注入した遺伝子治療でも起こることが示されており、胚の約 3 分の 1 が、交配前に注入された雄からの導入遺伝子を受け継いでいた[36]。遺伝子ワクチンを宿主細胞内に輸送するリポソームはエクソソームとしても作用し、スパイクタンパク質の遺伝コードを精巣および卵巣の細胞内に送達するが、そこでは生殖に重要な細胞内でスパイクタンパク質が合成される可能性がある。これらの組織のいずれかでスパイクタンパク質を合成する細胞に対する自己免疫炎症反応が起こると、胚細胞の死により不妊または妊孕性低下が引き起こされる可能性がある。さらに、ワクチン由来の遺伝物質がヒト肝細胞株で DNA に逆転写される可能性を示唆する in vitro データがあることから[37]、生殖組織を含む宿主組織に対する反応の可能性だけでなく、それらの配列が子孫に受け継がれる可能性についても考慮し、その可能性について徹底的に検討する必要がある。

5.病理組織学的データ

生検および剖検から得られた強力な組織学的エビデンスにより、ワクチン由来のスパイクタンパク質が終末分化組織で合成されたことが実証されている[38-42]。Baumeier らは、心筋炎が臨床的に疑われた患者(SARS-CoV-2 の検査は陰性であった)15 例中 9 例の心筋細胞でワクチン由来のスパイクタンパクを検出し、ウイルスタンパクが心臓組織で合成されたことを証明するとともに、ワクチン接種による自己免疫反応が示唆された[38]。Schwab らは、ワクチン接種から 20 日以内に予期せず死亡した 25 人(全ての鼻咽頭拭い液検体が陰性であり、ワクチン接種前に SARS-CoV-2 感染が確認されたか症状を呈していた死亡者はいなかった)に対して実施された標準化された剖検の病理組織学的所見について報告している[39]。前述の両研究は、ワクチン誘発性の心筋炎症は、自己免疫学的心筋傷害の主な要因である過剰な T リンパ球、主に CD4+T 細胞の浸潤の結果であるという考えを支持している。Mörz は、Pfizer 社/BioNTech 社のワクチンを接種した際に多巣性壊死性脳炎を発症した患者の脳および心臓に、ワクチン由来のスパイクタンパク質が発現していたことを報告した[40]。14 歳の日本人女性が Pfizer/BioNTech 社製ワクチンの 3 回目の接種を受けた 2 日後に死亡したが、先行する感染症、アレルギー、または薬物毒性への曝露がなかったことから、ワクチン接種後の多臓器炎症と診断された[41]。病理組織学的所見では、肺、心膜、心筋、肝臓、腎臓、胃、十二指腸、膀胱及び横隔膜に T リンパ球及びマクロファージの浸潤が明確に認められた。この研究では特異的な抗スパイク免疫染色法を用いなかったことを明記する必要があるが、T 細胞浸潤は上記の研究で観察されたものと同様のパターンを示し、2022 年 9 月 18 日に第 2 回医学シンポジウム「Current Findings on Vaccination Adverse Reactions」[42]で Arne Burkhardt 教授が提示した病理組織学的所見とも同様のパターンを示す。さらに、免疫組織化学検査により、ワクチンにコードされたスパイクタンパク質が真皮の小胞性角化細胞および内皮細胞に発現していることも明らかにされた[43]。

6.炎症のその他の原因

慢性炎症性脱髄性多発ニューロパチー(CIDP)や多発性硬化症(MS)などの一連の神経疾患は確実に診断されており、mRNA ベースの COVID-19 ワクチン接種が直接の原因とされている[44-47]。これらの症例では、ワクチンの mRNA によって産生された SARS-CoV-2 スパイクタンパク質の存在をルーチンの臨床診断で確認することはできないが、罹患神経組織内でのスパイクタンパク質の翻訳を支援する LINE-1(long interspersed nuclear element-1)および HERV(Human Endogenous Retroviral)を介した挿入機序によって説明することができる[48]。さらに、ニューロンにおけるスパイクタンパク質の毒性による p53 過剰発現の機序が最近明らかにされた[49]。p53 の調節異常レベルは、調節不全炎症反応の出現および自己免疫の発現と強く関連している[50]。さらに、mRNA ワクチンが自己抗体の産生を誘導し、その程度がワクチンへの曝露回数と直接相関すると考えられることが実証されており、免疫系の過剰刺激が自己炎症を引き起こす可能性があるという考え方が裏付けられている[51]。

血中の遊離スパイクタンパク質の存在[52-54]は、ACE2 結合を介してレニン-アンジオテンシン系の調節異常を引き起こす可能性があり[55-57]、内皮と血小板の相互作用[58]を引き起こして心血管系に害を及ぼす可能性があるため、さらなる危険の原因となる。

7.結論

多くの研究で、COVID-19 ワクチン接種後の自己免疫反応の発現が報告されている[47,59-76]。病理組織学的データからは、症候性の損傷を受けやすい終末分化組織においても、遺伝子ワクチンがオフターゲット分布を示し、スパイクタンパク質の合成を引き起こして自己免疫性炎症反応を誘発することを実証する明白なエビデンスが得られている[38-40,42]。抗原のプロセシングおよび提示の機序とウイルスタンパク質を合成する細胞への影響は広く知られており、何十年にもわたってその特徴が明らかにされてきた[13]にもかかわらず、遺伝子ワクチンはヒトにおける正確な体内分布と生物学的持続性の評価がなされないままに導入され、科学界の大多数は懸念を示すことなくそれを受け入れた。実際、2021 年に FDA に提出された Pfizer 社の非臨床概要の 20 ページ目には、「RNA またはタンパク質の代謝または排泄に関する試験は実施しない」と記載されていた[77]。さらに、2022 年 6 月 15 日に VRBPAC のメンバーである Dr. Jay Portnoy が提起した、スパイクタンパク質を産生する細胞数と mRNA 投与後のスパイクタンパク質の産生の量および持続性に関する質問について、Pfizer の代表である Dr.William Gruber は「学術的なもの」と一蹴した[5]。2022 年 6 月 23 日に ACIP の Dr.Pablo Sanchez が行った同様の質問に対して、Moderna 社の担当者は次のように回答した:「スパイクタンパク質のアベイラビリティは数日のオーダーであり、1 週間にも満たないようなものである。しかし、それについては毒性の担当者にも確認する。」[78]我々の知る限りでは、これはまだ利用可能になっていない。

さらに、パンデミック中に世界中の多くの国で施行され、表向きはウイルス伝播を制限する目的で剖検を実施しないという指針により、ワクチン関連死につながった可能性のある組織損傷の直接的エビデンスに関する臨床情報をより多く収集することが著しく制限された[79]。COVID-19 ワクチン接種と重篤な心血管合併症の発症との関連性は、特に若年層および健康な年齢層で広く認識されている[23,80-83]。剖検により、ワクチンにより誘発された病態が死因であったことが判明した研究が増えてきている[39,41,84,85]。一般に、LNP および mRNA の正確な分布と動態、ならびにスパイクタンパク質の産生を知らなければ、ヒト細胞を自己免疫攻撃の標的に誘導する遺伝子ワクチンの潜在的リスクを十分に評価することはできない。ヒトの体は厳密に区画化された系ではないため、ヒト細胞に非自己抗原の合成を誘導するすべての遺伝子ワクチン(現在開発中または将来開発される予定のもの)にとって、このことは深刻な問題である。実際、終末分化組織などの一部の組織では、細胞の喪失によって不可逆的な損傷が生じ、死に至る可能性のある予後がもたらされる。結論として、オフターゲット分布であることを示す否定できないエビデンスを考慮すると、COVID-19 に対する遺伝子ワクチンの接種は、正確な薬物動態、薬力学および遺伝毒性試験が実施されるまで中止するか、ベネフィット（便益）がリスクを大きく上回る状況でのみ行うべきである。

Author contributions

Conceptualisation, P.P. and P.Am; writing-original draft preparation, P.P.; writing-review and editing, P.P., A.D., J.C.L, D.W., A.K., M.M., P.B., M.F., S.S., P.Am; supervision, P.P. and P.Am All authors have read and agreed to the published version of the manuscript.

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【別紙資料7】

Autoimmunity

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Autoimmune inflammatory reactions triggered by the COVID-19 genetic vaccines in terminally differentiated tissues

Panagis Polykretis, Alberto Donzelli, Janci C. Lindsay, David Wiseman, Anthony M. Kyriakopoulos, Michael Mörz, Paolo Bellavite, Masanori Fukushima, Stephanie Seneff & Peter A. McCullough

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Autoimmune inflammatory reactions triggered by the COVID-19 genetic vaccines in terminally differentiated tissues

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ABSTRACT

As a result of the spread of SARS-CoV-2, a global pandemic was declared. Indiscriminate COVID-19 vaccination has been extended to include age groups and naturally immune people with minimal danger of suffering serious complications due to COVID-19. Solid immuno-histopathological evidence demonstrates that the COVID-19 genetic vaccines can display a wide distribution within the body, affecting tissues that are terminally differentiated and far away from the injection site. These include the heart and brain, which may incur *in situ* production of spike protein eliciting a strong autoimmunological inflammatory response. Due to the fact that every human cell which synthesises non-self antigens, inevitably becomes the target of the immune system, and since the human body is not a strictly compartmentalised system, accurate pharmacokinetic and pharmacodynamic studies are needed in order to determine precisely which tissues can be harmed. Therefore, our article aims to draw the attention of the scientific and regulatory communities to the critical need for biodistribution studies for the genetic vaccines against COVID-19, as well as for rational harm-benefit assessments by age group.

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1. Introduction

As a result of the spread of SARS-CoV-2, a global pandemic was declared by the World Health Organisation (WHO). The head of the WHO declared an end to COVID-19 as a public health emergency on May 5th, 2023; however, he stressed that it does not mean the disease is no longer a global threat [1]. The worldwide response to the outbreak focused on mass and indiscriminate vaccination using novel genetic platforms. Invoking emergency regulatory pathways to expedite market introduction, and the inherent public trust in traditional vaccines (based on inactivated or attenuated viruses), facilitated the use of lowered regulatory standards of safety and efficacy and circumvention of critical pharmacodynamic, pharmacokinetic and genotoxicity tests typical for drugs and gene therapies. Thus, billions of people were vaccinated despite a paucity of data regarding biodistribution or bio-persistence in humans, which only emerged from independent research or Freedom of Information disclosures after the administration of billions of doses. The speed at which the genetic vaccines were developed, manufactured and released was presented to the public as an achievement made possible by the scientific prowess of the pharmaceutical industry working in partnership with global governments for the greater good. However, in the words of the recently retired head of vaccine R&D at Pfizer, Dr. Kathrin Jansen: "*We flew the aeroplane while we were still building it*" [2]. This "achievement" involved scientific imprudence that must be subject to increased scrutiny as evidence of safety signals, negative vaccine efficacy and immune escape continues to accumulate.

The rationale behind this review article is to address the critical issue of the off-target distribution exhibited by the genetic vaccines against COVID-19, with a particular focus on the immunohistochemistry findings from histopathological studies. In fact, recent and conclusive sources of histopathological evidence demonstrate that the genetic vaccines against SARS-CoV-2 exhibit a distribution beyond the injection site that may involve terminally differentiated tissues subject to severe symptomatic injury. On the basis of a rational and unbiased assessment of the scientific evidence,

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and declaring that we have no conflicts of interest, we raise serious concerns regarding the safety of vaccination, especially for younger age groups and naturally immune who have a negligible theoretical benefit from vaccination. In fact, the former have a very low infection fatality rate [3], and the latter have a much higher protection against re-infection and severe COVID-19, conferred by natural immunity [4]. Therefore, the purpose of this article is to call the attention of the scientific and regulatory communities to the absolute necessity for pharmacokinetic and pharmacodynamic studies, as well as for rational harm-benefit assessments by age group.

2. The immunisation mechanism of the genetic vaccines

Many medical doctors and scientists currently recommending the COVID-19 genetic vaccines, might overlook key immunological mechanisms and underestimate the potential autoimmune consequences. Although this fact cannot be implicitly associated with hazard, even Pfizer does not fully understand how their vaccine works as Senior Vice President for Vaccine Clinical R&D Dr. William Gruber stated at FDA's VRBPAC meeting of June 15th, 2022: "*we don't have a complete understanding of the nature of the way that the vaccine works in terms of producing immune response*" [5]. The genetic vaccines against COVID-19 that were authorised for emergency use in the USA and in the European Union are the mRNA (nucleoside-modified) vaccines (produced by Pfizer/BioNTech and Moderna) and the adenoviral vector vaccines (produced by AstraZeneca and J&J/Janssen) [6,7]. These vaccines contain genetic information that hijacks human host cell machinery to synthesise the spike protein of SARS-CoV-2 and present it on the surface of cells as the immunogen [8–10]. Most likely, once translated by the ribosomes, the spike protein gets processed by the Golgi apparatus, and presented to the immune system in two ways: i) as the entire protein displayed on the cellular membrane, which can be recognised by B cells and T-helper cells; and/or ii) as protein fragments loaded on the major histocompatibility complex I (MHC I) [8,9,11].

All nucleated cells display the MHC I on their membranes, which present endogenous antigens, derived from the proteasomal degradation of intracellular proteins, to $CD8^+$ T lymphocytes [12–14]. This mechanism enables the immune system to monitor the proteosynthetic activity of all nucleated cells, in order to identify whether a cell is producing mutant, viral and/or non-self proteins, in general. The MHC II displays fragments of exogenous antigens that have been phagocytised throughout the body to $CD4^+$ T lymphocytes, and it is found on the membranes of professional antigen-presenting cells (APCs) [12,13]. When the immune system recognises a viral antigen as foreign, it triggers an inflammatory reaction which leads to the death of the antigen-presenting cell [12,13]. Consequently, the genetic vaccines, by inducing human cells to synthesise a viral protein, intrinsically rely on an autoimmune reaction mediated by T-cells to elicit an immune response.

3. Biodistribution beyond the injection site

Considering that every cell that synthesises viral proteins is perceived as a threat by the immune system and killed [11], it becomes crucial to determine the exact biodistribution of the genetic vaccines within the organism. Some authors pointed out the need for accurate pharmacokinetic and pharmacodynamic assessments [11,15–18]. However, despite the fact that pharmacokinetic studies are a fundamental part of drug safety assessment, according to European Medicines Agency (EMA) policy, they are generally not required for vaccines [16]. Thus, classifying these platforms as "traditional vaccines" allowed for such evaluations to be skipped [16,19]. It is well known that even "traditional vaccines" can cause the immune system to target its own cells throughout the immunisation process. However, there are some major differences between the genetic vaccines and the "traditional vaccines" for which the biodistribution evaluation is not "generally required". As was relayed in the letter by Polykretis and McCullough, the vaccines based on inactivated or killed viruses mainly involve presentation to APCs that phagocytose the virus particles and present the viral antigens to the immune system [20]. Such cells, which undergo a continuous turnover, perform this specific function within the organism, making them somewhat expendable. Regarding the vaccines based on attenuated viruses, they have a weakened virulence, resulting in the infection of a minor number of human cells in order to trigger an immune response.

A biodistribution study performed by Pfizer on rats and submitted to drug regulatory agencies, first released by Japan's Pharmaceuticals and Medical Devices Agency (PMDA), showed that the lipid nanoparticles (LNPs) containing the mRNA accumulate beyond the injection site, mainly in the liver, the adrenal glands, the spleen, the ovaries and other tissues [21]. Based on the findings of the aforementioned study (study No. 185350), regarding the biodistribution examined in rats injected with radiolabeled LNPs and luciferase modRNA, the Comirnaty (Pfizer/BioNTech) assessment report of the EMA, dated February 19th, 2021, on page 47, states: "*The radiolabeling data, measuring distribution to blood, plasma and selected tissues, of IM injection of a single dose of 50 µg mRNA over a 48-hour period is considered more sensitive than the bioluminescence method and indicate a broader biodistribution pattern than was observed with bioluminescence. Over 48 h, distribution from the injection site to most tissues occurred, with the majority of tissues exhibiting low levels of radioactivity*" [10]. Therefore, the EMA was aware that in rats a biodistribution beyond the injection site was occurring and that it was involving "*most* (selected) *tissues*". There is additional evidence that genetic vaccines can persist in the blood; Fertig et al. discovered that vaccine-associated synthetic mRNA stays in the bloodstream for at least two weeks following injection [22]. Notably, blood samples from children and young adults who developed post-mRNA vaccination myocarditis revealed the presence of circulating free spike protein [23]. Exosomes with spike protein have been detected in blood on day 14 after vaccination and increased after the

booster dose, lasting until four months [24]. Due to the principles of chemical kinetics and passive diffusion, the prolonged persistence of the LNPs containing the genetic material encoding the spike protein in the systemic circulation could enable it to reach even distant tissues. In support of this, the vaccine mRNA was detected even in secretions, such as breast milk [25]. Furthermore, it is noteworthy that the vaccine mRNA can persist in the lymph nodes up to 8 weeks [26], instead of "*few days*" as stated initially by the CDC [27].

4. A Role for exosomes

One mechanism by which the mRNA and the spike protein could be distributed throughout the body is *via* extracellular vesicles, particularly exosomes. A study preceding the release of the mRNA vaccines found that human cells exposed to mRNA nanoparticles were able to release fully intact mRNA molecules into exosomes, and that these exosomes could be taken up by recipient cells that then synthesised fully functional protein from the mRNA code [28]. Furthermore, an *in vitro* study demonstrated that human cells transfected with the mRNA nanoparticles coding for spike protein released the spike protein into exosomes that could then be taken up by microglia in the brain, triggering an inflammatory response [29]. In studies on biodistribution, very high concentrations among organs are found in the spleen. Immune cells in germinal centres in the spleen release exosomes as an essential step in antibody production [30]. Exosomes protect their mRNA cargo from degradation, and, furthermore, they not only travel freely *via* the vasculature and the lymphatic system, but they also easily navigate nerve fibres. *Via* travel from the spleen along the splanchnic nerve and the vagus nerve, they could reach major organs such as the heart, the liver and the brain [31].

Exosomal transport of genetic material also plays an important role in reproductive tissues such as the testes, where it has been demonstrated that a phenomenon known as Sperm-Mediated Gene Transfer (SMGT) occurs. This is the process by which genetic material from somatic cells in males can be passed on to progeny in an inheritable mosaic fashion, at low copy number, without needing to be stably integrated into the genome [32–35]. Recently, this phenomenon has also been shown to occur with gene therapies injected directly into mouse brain, where about a third of embryos inherited the transgene from the male being injected prior to mating [36]. The liposomes that traffic the genetic vaccines into the cells of the host also act as exosomes, delivering the genetic code for the spike protein into the cells in the testes and ovaries where the spike proteins could be synthesised in cells important for reproduction. An autoimmune inflammatory reaction against the cells synthesising the spike protein in either of these tissues, could result in sterility or decreased fertility due to the death of the germ cells. Furthermore, since there are *in vitro* data that suggest that the vaccine-derived genetic material can be reverse transcribed to DNA in a human liver cell line [37], we must not only be concerned about possible reactions against host tissues, including reproductive tissues, but we should also be concerned that these sequences may be passed on to the progeny, and we should thoroughly investigate such possibility.

5. Histopathological data

Strong histological evidence from biopsies and autopsies have demonstrated that the vaccine-derived spike protein was synthesised in terminally differentiated tissues [38–42]. Baumeier et al. detected the vaccine-derived spike protein on the cardiomyocytes of 9 out of 15 patients with clinical suspicion of myocarditis (which were negatively tested for SARS-CoV-2), proving that the viral protein has been synthesised in the heart tissue and suggesting an autoimmunological response due to the vaccination [38]. Schwab et al. describe the histopathological findings from standardised autopsies performed on 25 people who had passed away unexpectedly and within 20 days from vaccination (all nasopharyngeal swabs were negative, and none of the deceased persons had a recognised or symptomatic SARS-CoV-2 infection prior to vaccination) [39]. Both the aforementioned studies support the idea that vaccine-induced myocardial inflammation was a consequence of excessive T-lymphocytic infiltration, predominantly $CD4^+$ T-cells, which are the main drivers of autoimmunological myocardial injury. Mörz described the expression of the vaccine-derived spike protein in the brain and the heart of a patient who developed multifocal necrotising encephalitis upon vaccination with the Pfizer/BioNTech vaccine [40]. A 14-year-old Japanese girl died two days after receiving the third dose of the Pfizer/BioNTech vaccine and since there was no preceding infection, allergy, or drug toxicity exposure, the patient was diagnosed with post-vaccination multi-organ inflammation [41]. The histopathological findings clearly showed T-lymphocytic and macrophage infiltration in the lungs, pericardium, myocardium, liver, kidneys, stomach, duodenum, bladder, and diaphragm. It has to be specified that in this study no specific anti-spike immunostaining has been used; however, the T-cell infiltration displays a similar pattern with that observed in the abovementioned studies, and in the histopathological findings presented by Prof. Arne Burkhardt on September 18th, 2022, during the 2nd Medical Symposium, "Current Findings on Vaccination Adverse Reactions" [42]. Moreover, immunohistochemistry also revealed the expression of the vaccine-encoded spike protein in the vesicular keratinocytes and the endothelial cells in the dermis [43].

6. Additional causes of inflammation

A series of neurological disorders, including chronic inflammatory demyelinating polyneuropathy (CIDP) and multiple sclerosis (MS), have been firmly diagnosed and attributed directly to mRNA based COVID-19 vaccination [44–47]. Although routine clinical diagnostic measures cannot confirm the presence of SARS-CoV-2 spike protein, generated

by the vaccinal mRNA in these cases, they can be explained *via* Long Interspersed Nuclear Element-1 (LINE-1) and Human Endogenous Retroviral (HERV) mediated insertion mechanisms to support spike protein translation within the affected neural tissues [48]. Additionally, the mechanisms of p53 overexpression due to the spike protein toxicity in neurons has been recently revealed [49]. Dysregulated levels of p53 are strongly associated with the emergence of a dysregulated inflammatory response and development of autoimmunity [50]. Additionally, it has been demonstrated that mRNA vaccines induce the production of autoantibodies in extent that appears to be directly correlated with the number of vaccine exposures, supporting the notion that immune system hyperstimulation may result in autoinflammation [51].

The presence of free spike protein in the blood [52–54] constitutes an additional source of hazard since it may dysregulate the renin-angiotensin system *via* ACE2 binding [55–57], and could cause endothelia-platelet interactions [58], harming the cardiovascular system.

7. Conclusions

Numerous studies report the onset of autoimmune reactions following COVID-19 vaccination [47,59–76]. The histopathological data provide indisputable evidence that demonstrates that the genetic vaccines exhibit an off-target distribution, causing the synthesis of the spike protein and thus triggering autoimmune inflammatory reactions, even in tissues which are terminally differentiated and subject to symptomatic damage [38–40,42]. Despite the fact that the mechanisms of the antigen processing and presentation and the consequences for cells synthesising viral proteins are largely known and have been characterised for decades [13], the genetic vaccines were rolled out in the absence of accurate biodistribution and bio-persistence evaluations in humans, and the vast majority of the scientific community accepted that without raising concerns. Indeed, page 20 of Pfizer's non-clinical overview submitted to FDA in 2021 stated: "*No RNA or protein metabolism or excretion studies will be conducted*" [77]. Further, the question posed by VRBPAC member Dr. Jay Portnoy on June 15th, 2022 regarding the number of cells producing spike protein, and the amount and persistence of spike protein production after mRNA dosing, was dismissed as "academic" by Pfizer representative Dr. William Gruber [5]. A similar question asked by ACIP's Dr. Pablo Sanchez on June 23rd, 2022 was answered by the Moderna representative: "*The spike protein availability, I believe, is on the order of days, but like less than a week. But I will confirm that with our tox folks as well*" [78]. To our knowledge, this has not been made available.

Moreover, the guidance against performing autopsies, ostensibly to limit viral transmission, implemented by many countries worldwide during the pandemic, severely limited the ability to gather more clinical information regarding direct evidence of injuries in tissues which may have led to vaccine-related deaths [79]. The association of COVID-19 vaccination with the development of serious cardiovascular complications, especially amongst the younger and healthier age groups, has been widely recognised [23,80–83]. In a growing number of studies, it has been determined upon autopsy that vaccine-induced conditions were the cause of death [39,41,84,85]. In general, the potential risks of a genetic vaccine that induces human cells to become targets for autoimmune attack cannot be fully assessed, without knowing the exact distribution and kinetics of LNPs and mRNA, as well as the production of spike protein. Since the human body is not a strictly compartmentalised system, this is a matter of serious concern for every genetic vaccine (current or to be developed in the future) which induces human cells to synthesise non-self antigens. In fact, for some tissues, such as those terminally differentiated, the loss of cells results in irreversible damage with a potentially fatal prognosis. In conclusion, in light of the undeniable evidence of off-target distribution, the administration of genetic vaccines against COVID-19 should be halted until accurate pharmacokinetic, pharmacodynamic and genotoxicity studies are performed, or they should only be delivered in circumstances when the benefits greatly outweigh the risks.

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