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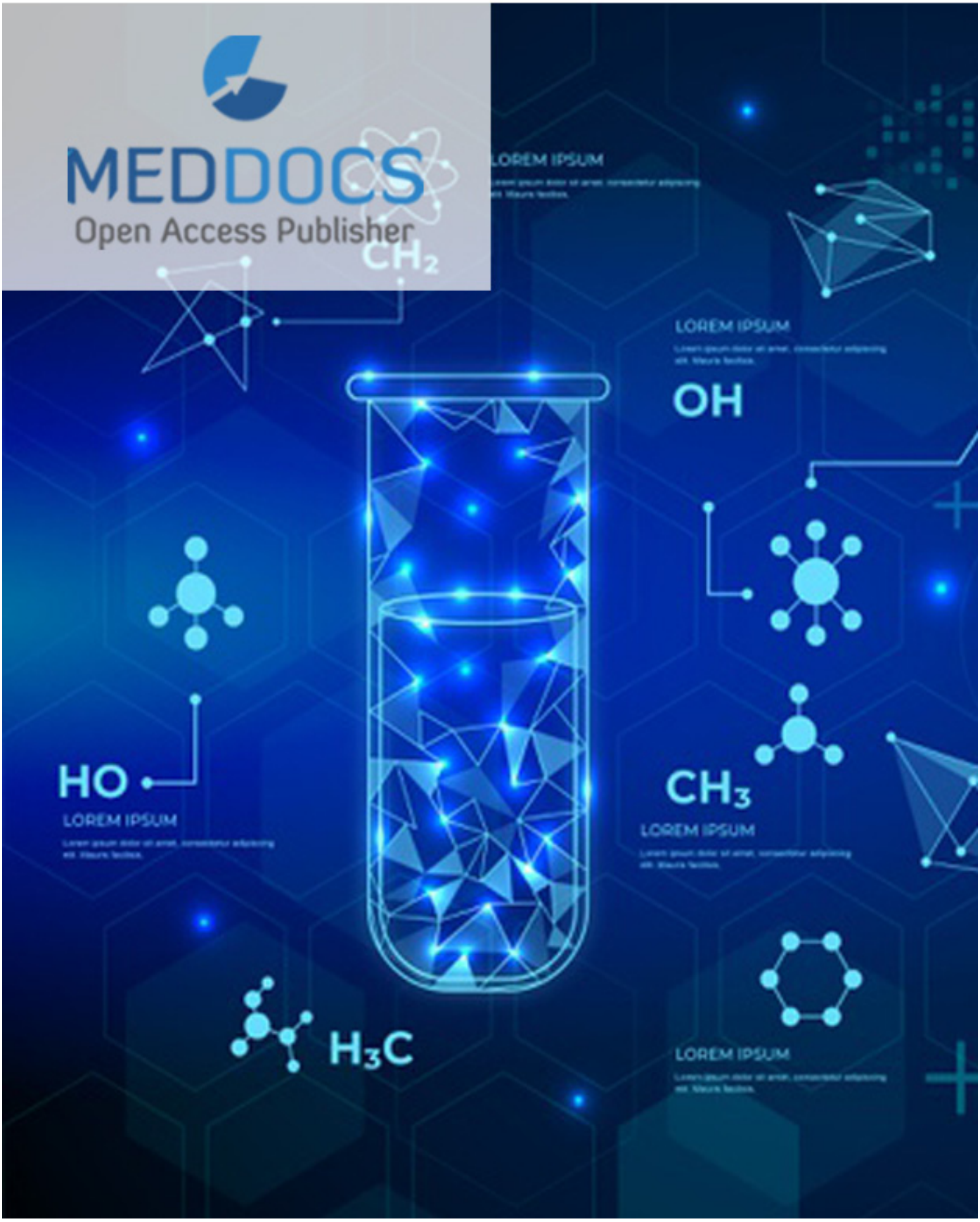

Aberrant Sialylation in Cancer Metastasis

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Abstract

Neoplasm metastasis is a multi-step and multi-level pathological feature causing 90% of cancer mortality due to a shortage of effective drugs and clinical therapeutics. To change this scenario, new drug targets and developments are required. Aberrant tumor sialylation as a putative drug target candidate has been evolving over the past half century. More recently, some specific agents and clinical events showed some promising therapeutic potentiality and benefits against neoplasm metastasis in a number of cellular and animal tumor models. Since neoplasm tissues often contain higher levels and diverse sialic acids (sia) analogues and antigens, sia-related tumor biology/pathology are emerging as cancer diagnostic categories and a series of useful agents until now. Previously some compounds enabling to inhibit sia-related pathologic pathways were reported to exhibit therapeutic activity in cellular or animal tumor models. These types of cancer treatment agents can provide excellent therapeutic outcomes by glycome/metabolomics diagnostics first. Taking together of these experimental/clinical discoveries, the "central dogma" of glycobiology might be found out via all these principle discoveries. In addition, mathematic- or physics-majored talents might render new therapeutic discoveries by computational analysis of experimental and clinical data. In this article, a line of patho-therapeutic events and relations is documented on this topic. Overall, therapeutic targets/benefits in the clinic should be pursuit with earnest attitude.

Backgrounds

Problem generations and clinical scenario for neoplasm metastasis

Cancer is the secondary frequent cause of disease-induced human mortality throughout the world [1-3]. Neoplasm metastasis is a fatal feature for treatment failures (approximately 90% of cancer deaths in the clinic). Despite great efforts, therapeutic benefits and developments against neoplasm metastasis by current drugs are futile until now [4-10].

Currently, anticancer drugs under clinical utility usually target on managing primary tumor growth rather than those specifically against metastasis lodging and outgrowth in distant tissues (invasive-metastasis cascades) and different levels of neoplasm pathways [8-10]. Finding sufficient anticancer drugs against neoplasm metastases in distant organs is indispensable in the future. It nevertheless needs to change unto drug target candidates against metastatic-related pathogenesis and human mortality. To attain this goal, updating anti-metastatic drug developmental systems must be carried out.

New orientation for anti-metastatic drug study

Generally speaking, antimetastatic therapy might be improved by a wholly understanding of metastatic biology and pathology in cancer patients [4-7]. The knowledge of pathophysiology stages, genetic heterogeneous, organ preferences, energy homeostasis and cancer plasticity may all contribute to therapeutic selection, drug responses and survival benefits in clinical trials [4-10].

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Before 2010, antimetastatic drugs being extensively studied were those mechanisms on antiangiogenesis and tumor stroma/matrix penetration (various types of metalloproteinase inhibitors [8-10]. These two types of tumor therapeutic agents are beneficial variability in different neoplasm subtypes, pathologic stages and seeding organ conditions/environments of cancer patients [6-11]. To make a metastatic cure, novel ideas, perspectives and even shotgun-like molecular expeditions seem indispensable. Experimental and clinical approaches based on biological/pathologic revelation of neoplasm metastasis, novel biomarker diagnostic categorizations and putative drug target candidates have been widely carried out since 2000 [4-11]. Dozens of such associations relevant to therapeutic promotions with sia-related pathways were proposed.

Aberrant sialylation in cancer pathology and drug developments

One of such cellular and molecular journeys has been the aberrant sialylation in neoplasm tissues and invasive-metastasis cascade in human body [12-16]. This complicated pathologic process has been insufficiently understood so far. To understand more, past discoveries must be referred with first.

Aberrant sialylation in neoplasia is an interesting pharmacologic topic that deserves strong financial and human resource supports. Some basic knowledge towards sialylation alterations in neoplasm tissues, metastatic outgrowth and potentiality as candidate drug target are highlighted, especially from broad-range of pharmaceutical and pharmacological expeditions.

Different ranges of patho-physiological characters on abarrant tumor sialylation

Biological discovery and common nomenclature

Sialic acids (Sias, neuraminic acid) are a special series of 9-carbon backbone negatively charged carbohydrates and typically found at terminal end of sugar chains attached to cell membrane glycoconjugates [14]. In early biologic discovery, they play critical roles in a great number of physiological and pathologic processes in many insects, reptile, animals and humans, including inter-molecular binding to initiate microbial infections, human immune response, tumor progresses/spreads and eventually in critical roles of biological evolutionary [17-19].

Scientific advances in neoplasia study

The earliest work unraveling the close relationships between sias and tumors traced back to Kimura et al in 1958 [20-21]. They discovered that tumor cells escalate their levels of sias-containing glycoproteins, glycolipids and other large biological molecules comparing with those sia-molecules in normal tissues. This particular type of biological/pathologic property was associated further with metastatic phenotypes (neoplasm spread and distant tissue colonization) [22-23]. Thence, numerous literatures showed biological similarity and diversity of a number of metastatic-related pathologic functionality, diagnostic categories and oncology aggressiveness [12-14]. Major cornerstone events of this series of biomedical research can be classified across history: (**Figure 1**).

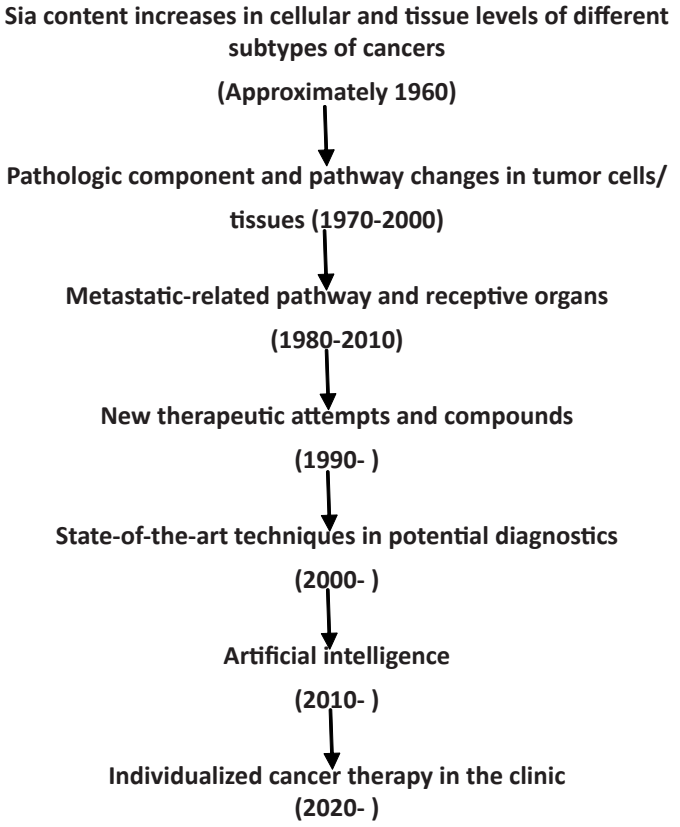

Figure 1: Evolution of patho-diagnostic systems between sialic acid changes and neoplasm progresses.

Sia-related pathogenesis in animals and patients with different cancers

Diverse sialic-acid contents and profiles in various cancer biology and pathology molecules

More than 60 different forms of sias mono-sugar have been found in nature until now. Given the character of diverse sia-analogues and tremendously complex sia-profiles can be found within 2-5 sugar component antigens (sugar chains) at the farthest end of cellular membrane antigens and glycoproteins in blood/lymphatic vessels of different organs [17]. Some of them, such as sialyl Lewis X and A are highly popular as tumorigenic antigens, associated with colon cancer, non-small cell lung cancer, pancreatic cancer and so on [19].

Landscape of patho-therapeutic relationships

The diverse features of cancer antigens and glycol-conjugates have been recommended as diagnostic categories and proposed as putative candidate drug targets for patho-therapeutic relation exploration at early stage in this moment. From pharmacological opinion, it is enormously significant for cancer etiology, biology, pathology, diagnostics, therapeutics and other clinical utility [12-14]. Similarly, some sia-containing antigens show a great biomedical significance in cellular/molecular biology [24]. In order not to duplicate similar studies, we neglect large body of literatures and basic glycol-terminology herein. Yet, the most important discoveries are depicted according to pathological pathways in **Figure 2 and Table 1**.

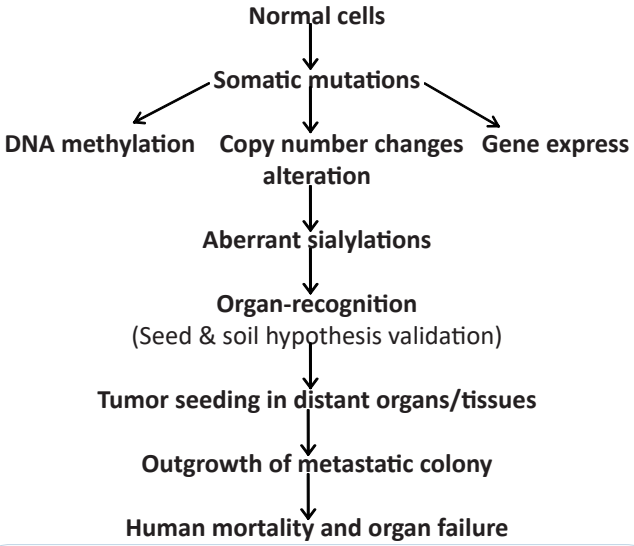

Figure 2: Schematic diagram of metastatic spreading-modes and distant organ colony formations by sialic acid related pathways and diagnostic potentiality.

"Seed and soil" hypothesis validation

The pathologic pathways, levels and cascades of neoplasm metastasis is complicated and multitude. The "seed and soil hypothesis" is a famous clinical evidence deserving molecular and biological verification. From a character of tumor colony in various distant organs, sia-related tumor recognizing systems may be an excellent pathway to associate with this hypothesis validation. Further projects and actions should be organized for verifying this hypothesis via sia-associated pathologic investigations and clinical data analysis and calculations.

Human sialyltransferases and sialidase as diagnostic biomarkers or putative drug target candidates

In advancing knowledge towards aberrant sialytion in tumor cells, one might immediately reflect with sialylation-related tumor enzymes in pathologic aggressiveness, invasion-metastasis cascade and potential therapeutic development. Sialyltransferases and sialidase as diagnostic biomarkers and putative drug's target candidates have been subjected to long-term scientific investigations as well as widely categorizing. All the structural and functional associations between sias chemical properties and tumor malignancy by different types of biologic enzymes are important avenues for enzyme-related cancer diagnostic/therapeutic studies. It adds in volume, complexity and expenditure of sia-related scientific study against tumor progression, invasion and remote metastasis. This kind of scientific exploration may be facilitated by broad-ranges of technical innovations and spectra of drugs in the future.

To face with this formidable challenge, cutting-edge biomedical technologies may help us to gradually understand patho-therapeutic relationship between sia-biology, diagnostics and therapeutics in new dimensions (different subtypes of cancer or metastasis stages/levels). Now, many sialyltransferases and sialidases have been widely classified [25-27]. Those structural and functional enzyme studies could add fresh and cumulative knowledge on cancer diagnostic and treatment options, such as basic biology/oncology, specific diagnostic modality, enzyme characters and therapeutic choices against neoplasm metastasis—including drug therapeutic index gains, tumor plasticity overcoming, seed and soil interaction, patient's survival benefits and many others.

Diagnostic modality in clinical situations

Sia-analogues in cancer biology and diagnostics

Early publications that N-glycolylneuraminic acid (Neu5Gc) is a cancer-specific carbohydrate in human pathology emerged over half a century [17-19]. This argument remains to be evaluated for cancer molecular biology and pathology. At this moment, this discovery has not been successfully translated into any workable diagnostic means in the clinic. Thus, we need to add new lines of its diagnostic evidence and valuable knowledge of patho-therapeutic relationship for cancer treatments. We have previously found that there is a different level and ratio of Neu5Ac, Neu5,9Ac and NeuGc in mice with different subtypes of tumors [28]. However, this kind of potential diagnostic measure is difficult to standardize and widely apply in the clinic because it needs expensive modern chromatography equipment and high-quality maintenance in pathologic labs of general global hospitals. However, things can be improved in the future.

Apart from sia-analogue and enzyme diagnostics, large volumes of sia-related bioinformatics data of both experiments and clinics greatly impact on cancer diagnostics and next generation of personalized cancer medicine. Technical innovation for sia-related cancer diagnostics and therapeutics is everywhere. Thus, we must keep pace with this technical character.

Different spectra of sia-analogue and conjugates for cancer pathological implication

We previously discovered that biological variations between analogue NANA and NeuGc at equal molar concentrations were found for calmodulin and peroxidant promotions in rabbit and human red cells [12-14]. Some other researchers also reported a variable activity between De-N-acetylneuraminic acid containing gangioside and acetylneuraminic acid containing gangiosides at same concentrations in cancers [30-32]. This is an interesting topic for cancer diagnostic/therapeutic study in the future. It provides compelling evidence for sia-related diagnostic-therapeutic relationship in nature and patients with different subtypes of cancers.

Table 1: Common associations between neoplasm progresses and sialic acid aberration.

Types	Analogues or conjugates	Pathologic pathways	References
Biology	Different sia analogues Glycoproteins Glycolipids Gangliosides Glycan Antigens (sialyl Lewis X) Sialytransferases Sialidase	Chemical structural diversity (>60 now) Biological molecular processes and signal pathways Cell regulation and diversity Cancer related pathways Cancer or metastatic related pathways Diagnostic or therapeutic importance Glyco-synthesis processes Glyco-decompose	[18-20] [30-32]

Pathology	NeuGc Sialytransferase activity Different conjugates	Commonly in human tissues Malignancy ongoing Different pathologic pathways	[36-40]
Diagnostics	Glyco-conjugate rise Different sia profiles Glycome Image techniques (PET) Detail bioinformatics	Poor pregnancy & tumor origin/subtypes Cancer biomarkers & biochemical mechanisms Tumor pathogenic origin and types Diagnostic or therapeutic values Detail diagnostic information Prognostic predictions	[29-33]
Therapeutics	Glyco- or antigen rise Cell-surface glycan change Detail bioinformatics Sialyl-antigen-derivatives Sialyl-transferase inhibitors	Antibody or lectin-based treatments Target anticancer drug developments Signal pathways Personalized cancer therapies Tumor inhibitions via physiological competitions Tumor inhibitions via blockage of key processes	[42-58]

There is a great duplication in sia-pathological literatures worldwide. This review cannot give full reference of most pathogenic and therapeutic studies. We suggest that readers can refer to many other sources of literatures and publications for this topic. **Table 1** just provides a snapshot of this topic and references. (**Table 1**)

Sia-content versus low pH value in tumor surface

An early well-known evidence that hypoxia may lead to low pH out-side of tumor surface. This raises an open question of whether an association between tumor biology and acidity is presence in nature [33-34]. Lower pH values in a lot of tumor surface might be caused from a general accumulation of sia (a series of negatively charged sugars). This possibly causal linkage provokes a new generations of tumor physiology of sia-character exploration in the future.

Bioinformatics of tumor sialic acids

Sia function and regulation in tumors

Given a possibility of multitude causalities of aberrant sialylation in tumors, we must break barriers on sia functional and regulatory mechanisms in malignant cells, especially in cancer cells/tissues for diagnostic/therapeutic purposes. More realistic diagnostic modality will be established and clinically validated via high-quality scientific projects.

Technology comparisons

Biomedical researches use broad-ranges of methodology. The commonest and sophisticated technologies for sia-tumor interactive and regulatory study were different types of glycome methodology in the past [35-40]. Glycome of sialylations is mainly designed by the utility of lectin/selectin-tumor interactions, bindings, immunohistochemistry, flow cytometry, molecular profiling or modern chromatography combined with mass-spectrometry. The majority bioinformatics techniques commonly need both modern separating systems/instruments (electrophoresis, high-performance liquid chromatography, HPLC or gas chromatography, GC) and state-of-the-art spectral validation systems (infrared spectra, IR, mass spectra, MS and others). In early sia-analogue study, HPLC and/or GC method combined with fluorescence and/or electro-conductive detectors for different sias analogue level determination are easy to reach, which are somehow more complicate than colorimetry evaluated for total sia concentrations in early stage of sia-study [29]. (**Figure 4**) This technique is a realistic sia diagnostic method for general hospitals worldwide yet unavailable.

Glycome analysis of sialylations

Diverse sias analogues (at least 60 subtypes) are discovered in nature until now, which are known for sure associated with life evolutionary and oncologic aggressiveness. Presently, cutting-edge technologies tell us a lot of biomedical/oncologic information of sia-related, especially the advent of glycome technology. In addition, these types of modern technologies, like glycome, proteomics, immuno-histochemistry and flow-cytometry categorization provide different information about altered cellular/molecular functionality and metastatic plasticity of sia-related in tumors comparing with early analytical systems (chemical analysis) and colormetry for total sia contents.

Despite great achievements, many types of glycome technologies are currently cumbersome and lack crystal-clear knowledge of patho-therapeutic relations. New round of technical innovations may shed new light for sia-related biological pathways, glycol-conjugates interaction/affinity, regulatory network and changeable metastasis states in different stages and locations from modern diagnostic establishments-sia-data mining and cellular signal integration. Besides, some other underestimated biological systems, such as genetic/epigenetic (DNA methylation, copy-number, genetic expressions and others) alterations of sialylations in tumors might prove to invite novel insights in the future.

Non-invasive diagnostic systems

More recently, imaging technology such as Positron Emission Tomography (PET) or PET-CT (computerized tomography) [41-42] plays biomedical diagnostic roles of cancers and other diseases in the clinic. Imaging diagnostic techniques are commonly non-invasive, which may reveal abnormal pathogenesis profiling in real-times and long course (long term patient's survival). Accordingly, this technology can facilitate the monitoring of sialic acid metabolism, regulation and outside interventions by using different radioisotope labeled sia- analogues or other enzyme substrates. Though it is difficult in diagnostic studies in human body with harmful impacts of unwanted radioactivity damages (radio-active element contaminations), it can be widely used for metastatic study in large animals by addition of higher doses and longer intervals of radio tracers without sacrificing the animals or invasive procedures of biopsy sampling from living bodies. This novel technical capability may accelerate sialic acids pharmacological evaluation and therapeutic landscapes against wide-spread of metastatic colony in living animal bodies. (**Figure 3**).

By PET-CT utility, we can evaluate and repeat record how tumor sia-related metabolisms and ongoing regulation in a great number of living animals with different subtypes of cancers for very long periods of time. As an outcome of this long term monitor, we can understand sia-abnormality in living bodies and change drug validation for both tumor inhibitions and survival benefits in animals, which is very useful in cancer treatment study and anticancer drug developments.

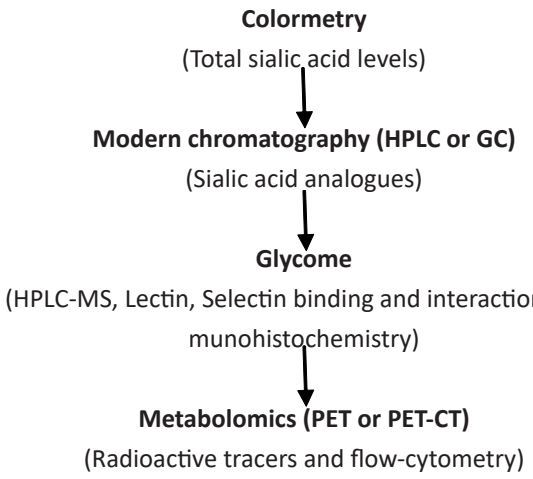

Figure 3: Methodology evolution of sialic acid pathologic/therapeutic studies.

Therapeutic study-activity and mechanisms

Past scenario

There is a long history of therapeutic study against sia-related tumor growth and metastatic outgrowth into distant tissues/organs worldwide [12-16]. It evolves from simple bioassays (total sialic acid content analysis) to in vitro anti-proliferative evaluation (drug sensitivity) to anti-metastatic responses into murine tumor models (Lewis lung carcinoma and melanoma B16) and finally enter into phase I clinical investigations (agent tolerance in healthy human bodies) [13-16]. The mechanistic and therapeutic studies for sias-related drugs began just at several labs approximately 30 years ago [29,42-45]. Nevertheless, this process of pharmacological validation (known anticancer agents against tumor-sias interaction and secretions in several tumor models) was unable to enter into drug markets due to lack of sufficient funds and devoted/talented pharmacologists. Until into this millennium, this series of therapeutic study was growing internationally.

The therapeutic difference for anti-metastatic efficacy between animals and human beings

In the early therapeutic study, the active sia antagonists against tumor growths were those of sias derivatives, conjugates and sias in bio-agents [42-45]. For example, some sia-conjugates can inhibit pulmonary metastases of a colon adenocarcinoma in mice [42-43]. But, these data are commonly identified in animal models, especially in murine models thereby diminishing their medical significance in the clinic. Now, people begin to note that antimetastatic agents identified in murine tumor models are usually inactive in real clinical settings [7]. Murine tumor models sometimes play a negative role of relations between animals and humans for therapeutic relevance, especially against neoplastic metastasis. In the future, large animals, such as dogs and monkeys will be used in anti-metastatic drug activity identification and evaluation including a number of sia-relative pathways and mechanisms.

Generally speaking, these sia-comjugate compounds are toxic for long-term toxicological evaluations among normal human beings [49]. As a result, it needs more cautious and scientific evaluations in the field of sia-related toxicological and therapeutic study. This major therapeutic difference against neoplastic metastasis between animals and human beings must be looked for and translated into clinical paradigms.

Similarly, a disaccharide linked sialyl Lewis X that inhibited tumor metastatic potential in vitro was also effective in experimental tumor model evaluations in mice [48]. Given into this complex situation between pharmacological data of animals and humans, how to find safe and highly effective sia-targeting drugs against neoplasm metastasis in humans are future priority and an indispensable part in anticancer drug developments.

Mechanisms of action

To harvest highly effective sia-targeted anticancer agents, mechanisms of action of these drug candidates are inevitable. To achieve this goal, general data of licensed drug against sia-pathways in experimental study were carried out in mice bearing tumors for both blood sias level inhibition and tumor weight inhibition (approximately 10 anticancer drugs). This experimentation aims at answering open question of whether anticancer drugs (especially antimetastatic activity) show some significantly associations between blood sias levels in mice and tumor growths in mice. This character of blood sia level inhibition varies in mice with different subtypes of tumor [29,47]. The highly antimetastatic agents, such as probimane show better blood sia inhibition comparing with other types of anticancer drugs in mice transplanted with several murine tumor models. The hidden rule behind this scenario needs to be found out. Other articles reports showed this identical character by plant extracts in mice bearing metastatic tumor models, like B16-F10 [51-52].

Table 2: The therapeutic models of serum sialic acid level changes in mice bearing B16F-10 by plant extracts [51].

Therapeutics	Schedule	Sialic acid μg/ml
Control (normal mice)	No tumor inoculation	21.3 ± 1.5
Tumor-bearing mice	Melanoma inoculation	108.26 ± 1.92
Sulforaphane	Simultaneously (drug)	35.13 ± 0.9
Sulforaphane	Prophylactic	59.51 ± 1.2
Sulforaphane	Developed metastases	92.88 ± 1.23

In agreement with early assumption, some licensed anticancer drugs such as 5-Fu that do not show typical antimetastatic effects also unable to inhibit sialic acid levels in mice bearing solid tumors (S180 and Lewis lung cancer) [55].

In enzyme activity bases, Chiang et al found that a novel sialyltransferase inhibitor (AL10) could decrease the functions of tumor adhesion, migration, actin-polymerization and other invasive phenotypes in cellular tumor modality. However, AL10 showed no anti proliferative efficacy in cancer cells [56]. This patho-therapeutic relation supports the hypothesis of sialic acid-tumor metastasis association in experimental data.

Moreover, sias-prodrug may enhance its uptake and cytotoxicity against tumor cell growths comparing with original drugs [57]. This pharmaceutical character of sia is an interesting topic for drug discovery and clinical relevance. (**Figure 4 and Table 3**).

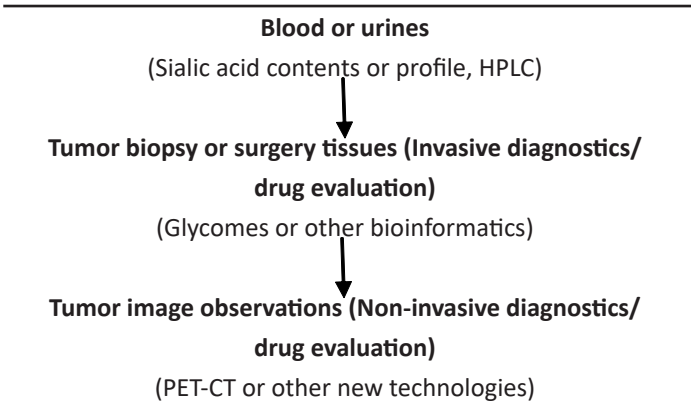

Figure 4: General routines in future experimental and clinical diagnostic/therapeutic evaluations.

Table 3: Outlook of anticancer agents or drugs in sia-related molecular targets and pathways.

Therapeutic types	Target or models	Reference
Sia-analog & derivatives	Bioassay Tumor inhibitions *in vitro* Metastasis inhibitions in animal tumor models Tumor apoptosis Chemical biology	[15,43-48]
Polymers	Clinical tolerance	[49]
Compounds	Serum sialic acid level in mice bearing tumor	[29, 50]
Polysaccharides	Immune promotions	[51-52]
Alkaloid from plant	Antimetastatic efficacy	[53]
Herbal drugs	Sarcoma	[54]
Drug combinations	Mechanisms	[55]
Novel compounds	Biochemical assay (Sialyl-transferase inhibitions)	[56]
Pro-drugs	Tumor affinity	[57]
Pharmaceutical innovation	Nanoparticle	[58-60]

Future road map

Biomedical and pharmacological studies of aberrant sialic acid (sialylation) in tumors are growing importance across the times [61-62]. They are very useful for clinical diagnostics, treatments and anticancer drug developments, especially anti-metastatic therapeutics [63-64]. We herein offer a line of pathologic evidence and cellular/molecular information towards this critical roles and associations between cancer aggressiveness and aberrant sialylation in tumor tissues and metastatic foci. Though many statements are given, a lot of questions remain to be answered. We select several key arguments, creative ideas and future challenges as follows.

- What are the exact oncologic pathways and regulatory network that may lead to aberrant sialylation in tumor progress and metastasis? Can we precisely control and regulate them back in the clinic?
- Diagnostic categories for sia-related technique updating to its reasonable price and anything that may lead to early diagnose for cancer metastasis stages, plasticity and drug resistances for individual cancer patients [65-73], especially in technical innovations [69-72].
- To some late-staged cancer patients, anticancer drug combinations are commonly more useful in the clinic. If sia-related agents are combined with other categories of anticancer drugs, may we expect favorable therapeutic outcomes for cancer patient's survival in the clinic? [74-76]
- Developments of more natural chemotherapeutic agents and drugs duo to commonly high-rate of therapeutic index. [77-78]
- More mathematical/computational analysis of experimental and clinical evidence/data will help streamline anticancer drug developments [79-88]. Across the history, many unexpected biomedical discoveries were coming from the cooperative studies between biomedical scientists and mathematic- and theoretic physicists [83-84]. What is the destiny of mathematical methodology in sia-tumor pathologic and therapeutic study?
- May cancer genomic study improve the study of aberrant sialylation in tumors [89-93]?
- Anything leading to therapeutic response and survival improvements, especially from sia pharmacological sides may become of a magic move towards a bright future.

Overall, we think that these questions are important to be understood. The rules of sias in nature and pathogenesis have enormously significance for cancer patient's survivals and medical maturation. (Table 5) The more we understand them in depth, the more therapeutic benefits (patient's survivals) we can be achieved.

Table 4: Future directions of sialic acid-related pathologic and therapeutic studies.

Categories	Methodology
Biochemical study	Medicinal chemistry Biochemical assay Mathematical simulations
Experimental evaluations in tumor cells	Tumor cell screening Genetic-modified tumor cells Drug develop study Tumor genomic study (next generation of sequencing, NGS) Mathematical study
Experimental evaluations in whole animals	Tumor inoculation sites or routes Therapeutic schedules Analytic chemistry (drug doses and metabolism) Toxicity study in animals (acute or sub-acute) Computational network
Pre- and clinical study	Drug tolerance and toxicity in animals and humans Absorption, metabolism, distributions and excretions GWAS Bioinformatics Analytical chemistry Tumor category or biological specificity Budget control and cost-effective Personalized medicines (DST, PG and neoplasm metastasis) Medication from multidisciplinary (teamwork) Global cooperation Computational network

Pharmaceutical challenge

Anticancer drug development

Until now, approximately 180 anticancer drugs are licensed worldwide [94]. Many different types of anticancer drugs are classified and marketed [95-122]. However, a lot of obstacles need to be overcome.

Anticancer drug development is waiting for new breakthroughs [123]. To achieve this ambition, creative ideas and drug targets must be identified and validated. With this character of diversity and complexity in nature, sia patho-therapeutic relationships among large populations of living bodies remain to be elucidated.

Sia-related pathology and therapy for drug developments

Therapeutic drugs targeting on different patterns of sia-related pathways and regulatory network in various tumor origins and subtypes might lead to new drug candidates and translate them unto clinical paradigms. It can expect wider capabilities of anticancer drug arsenal and clinical paradigms.

As the central dogma (rules and principles) of glycobiology is not well understood [79], some fundamental questions of carbohydrate itself [13-14] are even more meaningful comparing with sia-related disease treatment study at this moment. If we insist on translating biomedical knowledge into clinical practice (from bench to the bedsides), we are confident that a big difference can be made in the near future. The ultimate goal of complete cancer cure for all cancer patients is foreseeable.

Conclusion

A plenty of questions of solid associations between aberrant sias and tumor aggressiveness can be asked and answered. This needs time, fortune, new insights, talented scientists and dedicated clinical doctors. Correspondingly, advancing knowledge of biological/pathogenesis of neoplasm metastasis, sia-related mechanisms and matured antimetastatic therapeutics must be pursuit. In this critical moment, reshaping the strategy of antimetastatic drug developments and clinical treatment study, like aberrant sialylation in tumors is required to meet our growing intersts. Currently grim clinical situations call for new generations of sia-tumor relationship study in broader dimensions and complexity.

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