Applications of Biomarkers in Toxicology

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Abstract

Background: In any branch of toxicology it is important to be able to measure the exposure to a toxic agent, the extent of any toxic response, and also to predict the likely response. Tools that enable this to be done are called biomarkers. Therefore, in order to assess the health risks of exposure to potentially toxic chemicals, biomarkers are essential. Biomarker may be divided into: biomarker of exposure, biomarker of response or toxic effect and biomarker of effect.

Aim of the work: Introduce and establish the basic knowledge about biomarkers in toxicology for further researches, focusing on new biomarkers in toxicology and DNA adduct, biomarkers have role in in early diagnosis of organ toxicity and finally to know new application of biomarkers in toxicology.

Conclusion: In the field of toxicology, measurement of biomarkers reflects the time-course of an injury and provides information on the molecular mechanisms of toxicity. These biomarkers provide us the confidence of accurate diagnosis, prognosis, and treatment. The biomarkers of early chemical exposure can occur in concert with biomarkers of early disease detection, and that information aids in avoiding further chemical exposure and in strategic development of a novel treatment, including personalized medicine (i.e. treating the patient, and not the disease). In essence, with the utilization of specific biomarkers, an ounce of prevention can be worth a pound of treatment. In the toxicology field, biomarkers should be specific, accurate, sensitive, valid, biologically or clinically relevant, and easy and fast to perform in order to be useful as predictive tools for toxicity testing and surveillance and for improving quantitative estimates of exposure and dose. Therefore, biomarkers are utilized in biomonitoring data that are useful in a variety of applications, from exposure assessment to risk assessment and management.

Definition of biomarker:

The term "biomarker" a portmanteau of "biological marker, refers to a broad subcategory of medical signs that is objective indications of medical state observed from outside the patient which can be measured accurately and reproducibly. There are several precise definitions of biomarkers, and they fortunately overlap considerably. In 1998 the National Institutes of Health defined a biomarker as a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention (Strimbu and Tavel, 2010).

Criteria of ideal biomarker:

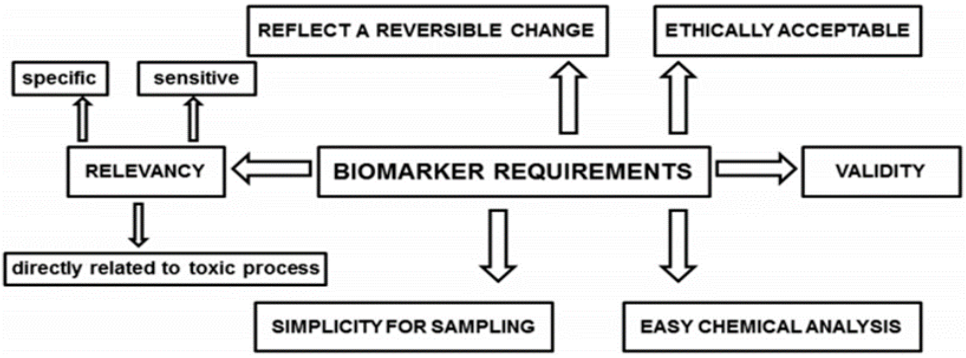

Figure (1) :
Requirements of a good biomarker in toxicological testing specifity (Gupta, 2014).

Definition of toxicogenomics

Toxicogenomics defined as the study of the relationship between the structure and activity of the genome and the adverse biological effects of exogenous agents. The term toxicogenomics encompasses transcriptomics, metabonomics, and proteomics (Aardema and MacGregor, 2002). Also, toxicogenomics defined as studying of cell structure and function in response to toxic compound. Transcriptomics are studying alteration of gene expression as a result of exposure to toxic compound . Metabonomics are studying the effect of toxic compound on cellular metabolic effect. Proteomics are studying alteration in level of protein expression in response to toxic compound (Au et al., 2011).

Agent toxicity biomarkers

In humans, exposure to chemicals in the environment (e.g. food, drinking water, air) can result in a series of events in the body. These changes observed as a continuum between external exposure and the resulting responses in the body (Link and Groopman, 2010). In examples, the measurement of lead levels in blood of the general population, especially in children before and after exposure. Other examples of successfully used biomarkers of exposure are for mercury in hair (for methylmercury toxicity assessment) to prevent methylmercury toxicity from contaminated fish consumption. Also ChE activity in RBCs and plasma to prevent neurologic effects from ChE inhibition. Finally urinary cotinine from exposure to second hand smoke or environmental tobacco smoke (ETS). The mercury and ChE activity measurements are used in toxicological risk assessments (Fan, 2014).

Applications of biomarkers in toxicology

1) Biomarkers in drug safety evaluation: Biomarkers are playing an increasingly important role in drug discovery and development from target identification and validation to clinical application, thereby making the overall process a more rational approach (Park et al., 2004). The incorporation of biomarkers in drug development has clinical benefits that lie in the screening, diagnosing, monitoring of the activity of diseases and in assessing therapeutic response. The development and validation of these mechanism-based biomarkers serve as novel surrogate end points in early-phase drug trials. The components of the biomarker development process include discovery, qualification, verification, research assay optimization, clinical validation, and commercialization (Rifai et al., 2006).The goal of incorporating biomarkers into clinical trials is to

manage a patient disease by administering effective and well-tolerated therapies, based on an understanding of the patient unique genetic and molecular profile (Zwierzina, 2008).

2) Biomarkers in biomonitoring of xenobiotics: Sometimes there are doubts as to whether or not an organism has been exposed to xenobiotics in the past, especially if exposure was not high enough to cause adverse clinical effects. Biomarkers of exposure allow the determination as to whether such organisms have been exposed or not, because the presence of xenobiotics or their metabolites in biological samples from the monitored individual is undoubted proof of exposure. Another advantage of biomonitoring is that biomarkers of exposure always refer to internal doses (once the xenobiotic has been absorbed) (Sogorb, et al 2014). Biomarkers of effect are very important for in vivo and in vitro toxicological testing as they are able to detect preclinical stages. Finally, biomarkers of susceptibility allow us to identify, among all the people in a given population, those individuals that are particularly susceptible to xenobiotics, which also would provide better protection of these individuals.

3)Biomarkers in computational toxicology: Computational toxicology is the application of mathematical and computer models and molecular biological and chemical approaches to explore both qualitative and quantitative relationships between chemical exposure and adverse health outcomes. Computational toxicology differs from traditional toxicology in many aspects, but perhaps the most important is that of scale. Scale in the numbers of chemicals that are studied, breadth of endpoints and pathways covered, levels of biological organization examined, range of exposure conditions considered and in the coverage of life stages, genders, and species. It will take considerable progress in all these areas to make toxicology a broadly predictive science (Kavlocketal., 2005).

4) Biomarkers of ecotoxicology: In the past, damage to the environment has largely been identified retrospectively and in response to acute events. Generally, these have been measured in terms of human health impacts and visible changes resulting from the loss of particular populations or communities. In practical terms, biomarkers are endpoints of ecotoxicological tests that register an effect on a living organism. There is, however, some confusion surrounding the use of the term biomarker. Many scientists view biomarkers merely as responses at the molecular, biochemical or physiological levels. While others take a wider perspective and include the accumulation of chemicals in the tissues of living organisms and even responses at the whole organism, population, community or ecosystem levels. One of the key functions of biomarkers is to provide an early warning signal of significant biological effects (Defra, 2004).

5) miRNA as a recent biomarkers: microRNAs (miRNAs), have been well recognized as reliable and robust biomarkers for early detection of diseases, birth defects, pathological changes, cancer, and toxicities. Because they are stable in biofluids, such as blood, there is rapidly growing interest in using miRNAs as diagnostic, prognostic, and predictive biomarkers, and the outlook for the clinical application of miRNA discoveries is promising, especially in molecular medicine. The application of miRNAs is still very new. Soon incorporating pharmacological and toxicological targeting of miRNAs into

the development of innovative therapeutic strategies will be routine.

Summary and conclusion

The term "biomarker" a portmanteau of "biological marker", refers to a broad subcategory of medical signs that is objective indications of medical state observed from outside the patient which can be measured accurately and reproducibly. The ideal biomarker should be ethically acceptable, easily sampled dependent on simple chemical analysis, reflect a reversible change, relevant, valid, specific and sensitive. The term toxicogenomics encompasses transcriptomics, metabonomics, and proteomics. Measurement of residues of pesticides and their metabolites, and metals in urine, serves as the most accurate and reliable biomarkers of exposure in agriculture, industrial, and occupational safety and health settings.

Biomarkers are playing an increasingly important role in drug discovery and development from target identification and validation to clinical application, thereby making the overall process a more rational approach. The advantages of biomarkers are well recognized by the research, medical and pharmaceutical communities. Biomarkers can reduce time factors and costs for Phase I and II clinical trials by replacing clinical endpoints. Biomarkers can also be helpful in redefining the diseases and their therapies by shifting the emphasis of traditional practices of depending on symptoms and morphology to a more rational objective molecular basis.

In the field of toxicology, measurement of biomarkers reflects the time-course of an injury and provides information on the molecular mechanisms of toxicity. These biomarkers provide us the confidence of accurate diagnosis, prognosis, and treatment. In the toxicology field, biomarkers should be specific, accurate, sensitive, valid, biologically or clinically relevant, and easy and fast to perform in order to be useful as predictive tools for toxicity testing and surveillance and for improving quantitative estimates of exposure and dose.

Recommendation:

1. There is need for introducing more knowledge about biomarkers in toxicology.
2. More focusing on new biomarkers in toxicology.
3. Introducing more and more technologies and instruments for identifying a lot of biomarkers.
4. Identify more about role of biomarkers for early diagnosis of organ toxicity.
5. There is need for more researches and data about miRNA to be used accurately in toxicology.

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الملخص العربي

- **تعريف الدلالات الحيويه:**

تعرف الدلالات الحيويه أو بمعني اخرالعلامات البيولوجيه بأنها مجموعه واسعه من العلامات الطبيه والتي تشير الي الحاله الصحيه التي تلاحظ علي المريض من الخارج وتقاس بشكل صحيح ومختصر.ولقد تم وضع تعريف للدلالات الحيوية بواسطة فريق عمل بالمعاهد الوطنية للصحة (NIH) بأنها مؤشر على العمليات البيولوجية التي تحدث في الجسم بسبب التعرض إلى دواء معين، حيث أنها تستطيع قياس هذه العمليات وتقيمها بطريقة موضوعية. وتعبر الدلالات الحيوية الجزيئية علي أي تغيير خلوي محدد يحدث علي مستوي الحمض النووي، RNA، التمثيل الغذائي، أو علي مستوى البروتين. وتشير الدلالات الحيويه الي مجموعه فرعيه من العلامات الطبية التي تلاحظ علي المريض والتي يمكن قياسها بدقة.

- **خصائص الدلالات الحيويه:**

سهوله الحصول علي العينه؛ سهوله التحليل الكميائي؛ مقبوله مهنيا؛ حساسه؛ مخصصه لكل ماده؛ ترتبط مباشره بالعمليه السميه وقابله للتقييم

- **تعريف علم الوراثه السمي:**

ويعرف علم الوراثة السمي بأنه دراسة للعلاقة بين مكونات المحتوي الجيني ونشاطه والتأثيرات البيولوجية السلبية التي تؤثر عليه عند التعرض لعوامل خارجية. ويشمل علم الوراثة السمي transcriptomics، proteomics،metabonomics. ويعرف أيضا بأنه دراسه للتغيرات التي تحدث لمكونات ووظائف الخلية عندما تتعرض لماده سامه خارجية.

Transcriptomics :عباره عن التغيير في التعبير الجيني نتيجة التعرض لمركب سام.

- **الدلالات الحيويه للعوامل السامه:**

عندما يتعرض الانسان لبعض المواد البيئيه السامه والتي يمكن تواجدها في الطعام؛ الشراب؛ الماء والهواء يؤدي ذللك الي حدوث سلسه من الاحداث بالجسم. علي سبيل المثال قياس مستوي الرصاص بالدم في مجموعه من الناس خاصه الاطفال قبل وبعد التعرض لماده الرصاص. ومن الأمثله الدلالات الحيويه الناجحه هي تحديد ماده الزئبق في الشعربعد التعرض لماده ميثيل الزئبق. وأيضا قياس مستوي انزيم AchE في كرات الدم الحمراء والبلازما في حالات التعرض للمبيد الحشري. وأخيرا قياس ماده الكونيتين في البول للأشخاص المعرضين للتدخين السلبي.

- **تطبيقات الدلالات الحيويه في مجال علم السموم**

1. **الدلالات الحيويه في تقييم أمان العقار:** وتلعب الدلالات الحيويه دور مهم جدا في اكتشاف الادويه وتطويرها وتطبيقها في المجال الطبي. وأيضا تلعب دور مهم في المجالات البحثية والطبية وعلم الأدوية. ويمكن

للدلالات الحيوية أيضا أن تقلل من عوامل الوقت والتكاليف الماديه أثناء المرحلة الأولى والثانية من االاختبار الاكلينيكي للدواء. تلعب الدلالات الحيوية دور مهم أيضا في إعادة مفهوم الأمراض وطريقة علاجها من خلال التركيزعلي التغير الجزيئ والذي يعتبر الأكثر دقة بدلا من التركيز علي علي المفاهيم التقليدية والتي تعتمد على الأعراض والعلامات التي تظهر علي المريض.

2. **الدلالات الحيويه في قياس المواد الخارجيه:** الدلالات الحيوية للتعرض تسمح بتحديد ما إذا كانت قد تعرضت تلك الكائنات لمواد سامه، لأن وجود هذه المواد أو نواتج تفاعلاتها في العينات البيولوجية من الفرد هو دليل لا شك فيه للتعرض. وهكذا فهي مناسبة لتقييم التعرض للمواد الخارجية خصوصا عندما يكون الكائن الحي ليس على اتصال مباشر بهذه المواد الخارجيه. أما الدلالات الحيوية للتأثير فتدل على وجود استجابة بيولوجية بسبب التعرض لهذه المواد الكيماوية. قد يكون هذا التعرض لعنصر داخلي بحيث يستطيع قياس القدرة الوظيفية ويقيس تغير بالنظام الحيوي والذي يعرف بحدوث عاهة أو مرض.وأخيرا الدلالات الحيويه للقابلية والتي تسمح بمعرفة الاشخاص الذين لديهم قابلية خاصه عند التعرض للمواد الغربية والتي توفر لهم حمايه خاصه للابتعاد عن التعرض لهذه المواد.
3. **الدلالات الحيويه وعلم السموم الحسابي:** ويعتبر علم السموم الحسابي هو واحد من الأبحاث المتزايدة والتي تظهر التقدم في البيولوجيا الجزيئية والكيمياء من أجل زيادة القدرة التنبؤية لمجال علم السموم. كما قامت وكالة الحماية البيئة بالولايات المتحدة بتعريف علم السموم الحسابي بأنه دمج تكنولوجيا المعلومات الحديثة مع علم الجزيئات لتحسين ترتيب الأولويات اللازمه لجمع البيانات وتقييم مخاطر المواد الكيميائية. في الوقت الحاضر، تستخدم التغييرات الزمانية والمكانية في النظم والمعايير البيولوجية المختارة لتعكس التغيرات في نوعية وظروف البيئة. وتقييم التعرض البيئي يمكن أن يتراوح من قياس المواد الكيميائية المتبقيه في أنسجة الكائنات الحية. ويعتبر استخدام الدلالات الحيويه شكلا من أشكال الرقابة القائمة على المواد الكيميائية.
4. **الدلالات الحيويه والتأثير السمي علي البيئه:** من الناحيه العلميه تعتبر الدلالات الحيويه من النقاط التشخيصيه النهائيه لمعرفه السميه البيئيه والتي تم تسجيل تأثيرهاعلي الكائنات الحيه.وتم عرض الدلالات الحيويه بواسطه العلماء علي انها تغيرات علي المستوي الجزيئي؛ البيوكيميائي أو الفسيولوجي وبينما الفريق الاخر يعتبر بأنها تراكم المواد الكميائيه في أنسجه الكائنات الحيه. ومن الوظائف الهامه للدلالات الحيويه كونها انذار مبكر للتغيرات البييولوجيه.