RESEARCH PAPER

Yh2ax As A Marker Of DNA Damage In Oral Precancer And Oral Cancer: Implications For Drug Delivery, Therapeutic Monitoring, And Clinical Outcomes

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Abstract
Oral squamous cell carcinoma (OSCC) is a multistage carcinogenesis that is initiated by oral potentially malignant disorders, as a result of cumulative DNA damage and genomic instability. To enhance the result of treatment, it is crucial to identify feasible biomarkers capable of linking the biology of the disease with the evaluation of its treatment to assess whether the disease was fixed or developed into a completely functional cell. γH2AX, which is a phosphorylated form of histone generated in response to the activity of breaks on the DNA strands, has become a sensitive measure of cellular damage and repair processes. This review is a critical analysis of the role of γH2AX in oral precancer and cancer with a focus on its growing use in drug delivery and pharmaceutics. It has been shown that, the expression of γH2AX rises gradually through normal mucosa, dysplasia and carcinoma as a prognostic of tumour aggressiveness and treatment outcome. Notably, γH2AX is a pharmacodynamic biomarker of assessing the efficacy of chemotherapeutic agents, radiotherapy, and targeted therapies. Its incorporation into nanotechnology-based systems of drug delivery and controlled release formulations can serve as a quantifiable endpoint of the evaluation of drug performance and therapeutic optimization. It can also be used to develop pathway-based targeted therapies as this, in combination with the fact that it relates to DNA damage response pathways. As a whole, γH2AX provides an opportunity in the connection of molecular diagnostics with sophisticated drug delivery methodology, which will improve accuracy of treatment in the treatment of oral cancer.

Keywords: γH2AX; Drug Delivery, Oral Squamous Cell Carcinoma, Nanocarriers, Pharmacodynamic Biomarker
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1. Introduction

OSCC is a major health challenge in the world since it is prevalent in locations where tobacco use, alcohol consumption and betel nut chewing are high and ends with the ultimate genetic alterations and unremitting damages to the DNA leading to malignant transformation[1].

Regardless of the additional diagnostic and treatment strategies, OSCC remains a low prognosis after late-stage representation and low efficacy of the conventional therapy, therefore, requiring the addition of molecular biomarkers and the advanced drug delivery options to enhance the instrument of earlier diagnosis, therapy localization, and patient outcomes[2].

In the last few years, Nanosystems of drug delivery through nanotechnology have significantly enhanced the targeted delivery of chemotherapeutic compounds, and have resulted in enhanced bioavailability, reduced systemic poisoning and enhanced therapeutic effect of delivery of orally introduced chemotherapeutic agents[3]. Liposomes, polymeric nanoparticles and metallic nanoparticles are examples of nanocarriers that have shown potential as anticancer drugs delivery vectors that target specific tumor tissue, as well as had shown advantages by overcoming the negative side effects and potential toxicity limit of the traditional methods of delivery and administration[4].

Within the emerging pharmaceutics, the method of drug delivery and response to treatment has acquired increased importance of determining valid pharmacodynamic biomarkers, which are capable of measuring drug delivery and cause cell damage in real-time clinical application[5].

H2AX, a phosphorylated form of the histone variant H2AX, γH2AX at serine 139, is deemed an extremely sensitive DNA strand break repair data and an important

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part of the cellular DNA damage response cascade, and therefore a convenient measurement of genomic instability and cytotoxic effects of treatments[6].

Another evidence that is emerging to indicate that the level of γH2AX expression increases gradually between normal mucosa of the mouth and dysplastic lesions and increases exponentially in OSCC represents the accretion of the DNA damage and its close relationship with the tumor progression, invasiveness, and the ability to metastasize[7].

Further, γH2AX can also interact with key molecule regulators, such as p53, ATM, CHK2 and BRCA1, indicating its primary position in the repair of DNA damage, and its potential use in the framework of the evaluation of the effectiveness of targeted drug delivery system which is aimed to induce selective destruction of DNA in cancer cells[8].

It is interesting to note that γH2AX has been explored to be a predictive and prognostic bi- marker in oral cancer in which the levels of expressions have been associated with treatment response particularly in radiotherapy and chemotherapy resulting in clinicians the ability to monitor treatment response and thus differentiating between treatment regimens[9].

These qualities can inform its application of γH2AX in drug delivery inquiry as a new way to bridge the molecular oncology and pharmaceutical disciplines by providing an appraisable end point of measuring drug activity, better-controlled and directed models of delivery and the approaches of precision drug development in the cure of oral cancer[10]. The objectives of this review are:

1. To assess γH2AX as a biomarker of DNA damage in oral precancer and oral cancer
2. To evaluate the role of γH2AX in drug delivery systems for monitoring therapeutic efficacy and optimizing treatment

2. Review Methodology

To integrate the existing evidence of the literature on the subject of the γH2AX expression in oral precancerous lesions and oral squamous cell carcinoma (OSCC), in particular, its usage in drug delivery and therapeutic monitoring, a detailed narrative literature review was conducted. Electronic databases, including pubmed, scopus and web of science among others, were searched using keywords, including, but not limited to, the γH2AX, DNA double-strand breaks, oral cancer, oral dysplasia, drug delivery, nanoparticles, and pharmacodynamic biomarkers, up to 2025.

The inclusion criteria were that the peer-reviewed article was an original research article or a review article that addresses γH2AX expression in oral potentially malignant disorders (OPMDs) and OSCC; and studies assessing responses to DNA damage caused by either chemotherapeutic agents, radiotherapy or advanced drug delivery systems. The study of γH2AX as a biomarker to assess the effectiveness of treatments, controlled drug delivery and the delivery of drugs to specific target sites was given special attention.

Articles were filtered by them due to not being in English, not being peer reviewed, case report, and not being relevant to either oral carcinogenesis or drug delivery use. Narrative as opposed to statistical meta-analysis because the literature analysis was critical and synthesized to guarantee such consistency, since the review was exploratory and integrative. Such a strategy made it possible to integrate the expertise on the molecular, clinical, and pharmaceutics with an additional role of the biomarker to optimize the diagnostics and optimization of drugs delivery technologies.

3. Molecular Basis of γH2AX in DNA Damage and Repair

H2AX, a phosphorylated derivative of the histone protein H2AX, forms quickly and at DNA break sites, and is a sensitive and early sign of DNA damage and genomic instability in a range of disease pathologies, including cancer[11].

Such pharmacognosy must recognize and induce the activation of the DNA damage response by phosphorylation of H2AX at serine 139 that allows the identification of the presence of the damage to the DNA and signaling to ensure the preservation of genomic integrity.

Due to the broken repair pathways, continued expression of γH2AX even with background defective DNA repair, has been attributed to overemphasized cell sensitivity to radiation, especially in cancer treatment patients receiving radiotherapy[12].

The γH2AX foci are sites of recruitment of most DNA repair factors, including CHK2, BRCA1, and p53 to form repair complexes and activate downstream signaling pathways that have roles in cell cycle regulation and inhibiting apoptosis[13].

Besides its effects in acute DNA damage response, it has been reported that γH2AX is also engaged in a large number of physiological processes which implies that it is more broadly applicable in the maintenance of genomic stability in cell development and aging processes as shown in Table 1.

The microenvironmental factors of hypoxia also contribute to the regulation of the γH2AX expression to remodel the effectiveness of DNA repair and to contribute to the heterogeneity of tumors, and this effect was also used on the responsiveness of therapy and resistance to cancer development[15].

Table 1: Role of γH2AX in Drug-Induced DNA Damage and Therapeutic Evaluation

Therapeutic Agent/System	Delivery Type	Mechanism of Action	γH2AX Response	Clinical/Pharmaceutics Implication (Refs)
Radiotherapy	Localized radiation delivery	DNA double-strand breaks	Increased foci formation	Radiosensitivity assessment[16]

Targeted therapy (PARP inhibitors)	Oral/systemic targeted delivery	Inhibition of DNA repair pathways	Enhanced γH2AX accumulation	Therapy optimization[17]
Chemotherapy (Cyclophosphamide + Veliparib)	Combination drug delivery	DNA damage + PARP inhibition	Elevated DNA damage signaling	Improved treatment efficacy[18]
Flavonoid-based therapy (Apigenin)	Natural compound delivery	Induces apoptosis via DNA damage	Increased γH2AX expression	Antitumor potential evaluation[19]
Prognostic biomarker application	Diagnostic/monitoring system	DNA damage response signaling	Persistent γH2AX levels	Survival prediction and prognosis [20]

Collectively, these molecular events reveal that γH2AX plays the central role in DNA damage signaling and repair, and the genomic instability is linked to cancer progression and provides a mechanistic foundation to its application in the measurement of drug-induced DNA damage and optimization of the targeted therapeutic strategies.

4. γH2AX Expression in Oral Precancer and Cancer

4.1 Expression in Oral Potentially Malignant Disorders (OPMDs)

It has been demonstrated that the expression of γH2AX increases gradually with expression in normal oral mucosa and varying levels of epithelial dysplasia that are indicative of the accumulation of DNA damage during the early stages of carcinogenesis[21]. This biomarker has a very low level of expression in normal tissues, but is evident in basal and parabasal layers in case of mild dysplasia and this is an early sign of genomic instability. When dysplasia progresses to moderate and severe levels, the count and the localization of γH2AX-positive nuclei go up in the layers in the epithelia indicating that the double-strand breaks in DNA and repair systems are exacerbated. To a large extent, these patterns of expression are inextricably linked to the risk of malignant transformation and γH2AX is a useful device to forecast high-risk OPMDs.

Much more, it has been linked to other proteins of the DNA damage response, which further support its role in the initial molecular alterations preceding development of overt malignancy. By doing so, γH2AX may serve as a diagnostic biomarker and as a tool to stratify patients by transformation risk.

4.2 Expression in Oral Squamous Cell Carcinoma (OSCC)

Our findings reveal that γH2AX expression is very high in OSCC compared to the normal mucosa and the dysplastic lesions and this is a sign of broad genomic instability and incessant DNA damage. The higher γH2AX levels correlate with high tumor grade, high aggressive behavior and high invasive potential, meaning that it is very applicable in tumor progression.

Moreover, both γH2AX expression and lymph node metastasis have been observed to be significantly correlated and therefore, the γH2AX expression is a useful prognostic biomarker in a clinical setting. Large foci of γH2AX occur in tumor cells, and this suggests sustained activation of the DNA damage response, and it can be triggered by both internally acquired genetic modifications and externally administered therapeutic treatment. The findings demonstrate the importance of γH2AX in tumor biology research, in addition to the evaluation of disease severity and progression[22].

This implies that γH2AX can be utilized as a treatment monitoring and prognosis biomarker in the case of OSCC and, therefore, it can be incorporated into a complex strategy of drug delivery and treatment assessment[23].

5. γH2AX as a Pharmacodynamic Biomarker in Drug Delivery

5.1 Evaluation of Chemotherapeutic Drug Action

As a result of chemotherapeutic agents, including cisplatin, doxorubicin, and alkylating agents, DNA breaks in the form of double strands are induced resulting in the activation of cellular pathways of DNA damage response culminating in the eventual death of cancer cells[24], as shown in Figure 1. The γH2AX pharmacodynamic biomarker is highly sensitive and enables the detection of such lesions at an early stage following the exposure to drugs. foci formation of the γH2AX are directly correlated with the extent of the DNA damage, and therefore, good predictor of treatment success in cancer.

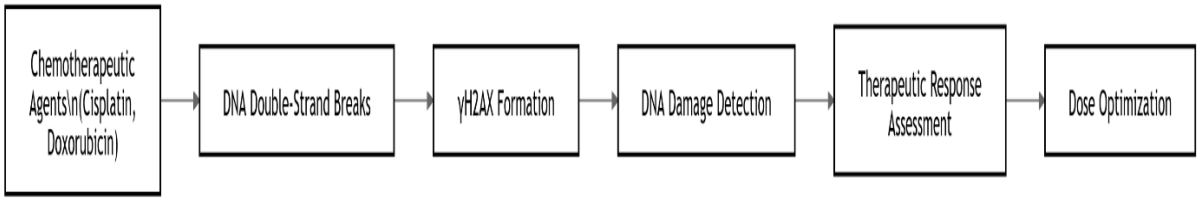

Figure 1: Schematic Representation of γH2AX-Mediated Evaluation of Chemotherapeutic Drug-Induced DNA Damage and Therapeutic Response

This allows the clinicians and researchers to assess the workings of the drug at the molecular level and hence make the treatment plans better. Moreover, γH2AX-based assays help to optimize the chemotherapeutic dosage regimes to kill tumor cells to the utmost, and reduce the toxicity to the minimum.

5.2 Monitoring Radiotherapy Response

Radiotherapy continues to be part of the foundations of cancer treatment and its therapeutic actions are largely based on the induction of DNA base strand breaks in cancer cells[25].

H2AX phosphorylation to γH2AX is a rapid reaction to radiation and therefore it is a useful biomarker to determine radiation damages in DNA[26]. The amount of DNA damage as well as the effectiveness of repair mechanisms in irradiated cells can be researched using the γH2AX foci in a quantitative manner. This enables the clinicians to determine the radiosensitivity of the tumours and provide a clue on how a certain patient would respond to a certain treatment. Consequently, γH2AX surveillance can be useful in improving the personal radiotherapy planning by informing adaption in dose and improving delivery of treatment.

5.3 Role in Targeted Drug Delivery Systems

The objective of targeted drug delivery systems is to enhance tumor tissue therapeutic effects through specific targeting of anticancer drugs at tumor tissues but without causing systemic side effects. Their ability to induce sufficient damage to the DNA strands within the cancer cells that can be detected using gamma H2X as one such biomarker can be tested to determine the functionality of these systems[27,28], as also presented in Table 2. This especially applies in the development of nanocarrier and molecule-directed therapy. The γH2AX-based model of drug delivery effectiveness and biological reaction is a highly useful instrument in the process of validation and optimization of targeted therapeutic modalities.

Table 2: γH2AX in Drug Delivery and Therapeutic Evaluation

Therapy/System	Delivery Type	Target/Pathway	γH2AX Role	Implication
Radiotherapy	Ionizing radiation	DNA DSBs	Foci formation	Damage quantification[29]
High-dose irradiation	External beam	Radiosensitivity	Residual foci	Response prediction[30]
DDR biomarker panel	Molecular profiling	PARP1/BRCA1	Expression levels	Survival prediction[31]
DDR-targeted therapy	Targeted drugs	DNA repair pathways	Increased signal	Therapy advancement[32]
ATR/CHK1/2 inhibitors	Targeted therapy	Replication stress	γH2AX activation	Precision targeting[33]

6. γH2AX in Nanotechnology-Based Drug Delivery

The creation of nanotechnology-based drug delivery system has been a potential treatment in cancer treatment wherein therapeutic agents are transported to the tumor in the body through the delivery system with great precision and moreover, the bioavailability of drugs is also increased. These systems include liposomes, polymeric nanoparticles and hydrogel based carriers that allow the controlled release of drugs and targeted location of their release and this system is better as it enhances the efficiency of therapy and minimizes the systemic toxicity[34].

Some of the mechanisms that can result in the DNA damage of cancer cells by the Nanoparticles include oxidative stress, generation of reactive oxygen species, and disruption of DNA repair pathways. Such nanoparticle-induced genotoxicity can be conveniently assessed with the help of γH2AX that is a sensitive assay of DNA double-strand breaks and cellular stress responses[35].

One of the tools that is applicable in studies of nanomedicine to identify the cytotoxic efficacy and pharmacologic efficacy of advanced drug delivery mechanisms is the application of γH2AX analysis. Mapping the γH2AX expression is provided by the DNA damage caused by nanoparticle, which allows the researcher to optimize the system of delivery so as to target the protein in a more accurate location and to release it whenever it is required.

Thus, a significant role in the relationship between nanotechnology and pharmaceutics is the γH2AX which offers safer and effective targeted therapy in the management of oral cancer.

7. Role of γH2AX in Controlled and Sustained Release Systems

Process Controlled and sustained delivery systems are used to ensure therapeutic levels of drugs, over a more extended duration, and increase treatment efficacy and reduce dosing frequency of oral cancer treatment. These systems ensure that the tumor cells have prolonged lives of the chemotherapeutic agents that augment the induction of DNA injuries and curative results[36].

γH2AX is an appropriate pharmacodynamics biomarker that can be used in the measurement of the long-lasting DNA damage when the systems are subjected to a continuous exposure to a drug. Its expression reveals the preservation of the DNA interrupts of the two strands of the DNA strands, and permits the indirect determination

of the kinetics of the drug release and the intracellular drug activity over time[37].

The relationship between the level of γH2AX and chronic exposure to therapy allows researchers to estimate the efficacy of controlled release preparations and plan them to produce the most intense cytotoxic effect (Figure 2). This applies in particular to advanced drug delivery mechanisms where maintaining a constant amount of drug in the body is significant in the provision of the desired therapeutic effect.

Figure 2: **γH2AX-Guided Evaluation of Controlled and Sustained Drug Delivery Systems**

Thus it can be restated that the γH2AX analysis as part of the experiments of the controlled drug delivery is a robust solution to maximize the dosage regime or efficacy of the particular curing technique and improve the overall clinical outcome of the cancer treatment.

8. Integration with Molecular Pathways for Drug Targeting

Integration of γH2AX and fundamental pathway in the DNA damage response presents a strong mechanistic foundation of targeted drug delivery methodologies in cancer treatment. Centrally regulated by the kinases ATM, ATR, and DNA-PK, the signalling events that control the detection of DNA double-strand breaks and initiate downstream signalling cascades, including CHK2 and p53, are all important to ensuring cell cycle arrest, repair or apoptosis[38].

The γH2AX action in this pathway is that it is an initial signal to recruit repair factors, like BRCA1, to enhance this signal, which is entirely required between the identification of molecular damage and targeting of therapeutic actions..

This discovery of these pathways has led to new modes of treatment, especially the use of PARP blockers that exploit the genetic defects in the homologous recombination repair mechanism, which induces synthetic lethality in cancer cells with impaired DNA repair mechanisms[39].

At the same time, the γH2AX with other biomarkers such as p53 and p-ATM can be utilized to offer a multidimensional measure of treatment response to improve precision in treatment delivery.

By so doing, integrating γH2AX in the DNA damage repair networks will contribute to developing the complex drug delivery and combination therapy that will enhance their therapeutic effect and decrease drug resistance.

9. Clinical and Pharmaceutics Applications

The γH2AX has become an important biomarker in the clinical oncology field as well as in drug development with reference to measuring drug efficacy and the optimal therapeutic regimens. γH2AX is frequently applied in preclinical drug screening to determine the DNA-damaging potential of new compounds which are useful in the case of anticancer drug development. The quantitative measure of its value is a valid pharmacodynamic endpoint to compare the various drug formulations and administration systems. γH2AX has the potential to be used in personalized medicine to predict the specific response and repair ability of various people by showing changes in DNA damage response and repair. Also, the γH2AX levels can be monitored in response to treatment to early identify therapeutic resistance, which can be used to adjust treatment programs in time. It is also useful in stratification of high-risk patients, which is the identification of patients with severe genomic instability. Moreover, the application of γH2AX as a vital biomarker has been used in clinical trials that use advanced drug delivery systems to determine treatment response and confirm the effectiveness of the targeted and controlled drug delivery strategies.

10. Challenges in Translating γH2AX into Drug Delivery Research

Despite this promising application, there are other obstacles to the overall application of γH2AX in drug delivery research. This is because of the lack of standardized protocols of detection and quantification which are one of the most critical issues since they can lead to the variability of results in various studies and labs. The differences in sample preparation, specificity of antibodies and imaging also contribute to the differences in γH2AX measurements. Also, γH2AX is not entirely cancer specific DNA damage, as it can also result due to physiological stress or inflammation or environmental agent and it can be interpreted with difficulty in clinical practice. The other weakness is that, no scoring systems are universally accepted thus, findings could not be easily compared across studies. In addition, there is still a lot of clinical validation required to ascertain its reliability and repeatability in connection to being a pharmacodynamic biomarker. These issues should be overcome so as to integrate γH2AX into the drug delivery and therapeutic monitoring models.

11. Future Perspectives

It is foreseen that the application of γH2AX in additional therapeutic use and drug delivery would be prolonged in the future research. The combination of γH2AX systems and nanomedicine platforms leaves the room to produce delivery systems that can be dynamically traced basing on the real-time analysis of the DNA damage. The use of the γH2AX patterns can be further improved as a result of the new technologies, including artificial intelligence and machine learning, that would be created, allowing to predict the outcome of the treatment. Adaptive strategies that react to tumor-specific levels of DNA damage through the use of a system that responds to γH2AX-guided delivery of therapeutic agents could be developed. Moreover, γH2AX analysis along with some molecular treatments such as repair inhibitors may also lead to more specificity and efficacy of treatment. The technology also allows the use of innovations to monitor non-invasive and real-time γH2AX in clinical practice through the use of biosensing technologies. All these tests indicate that gammaH2AX has the potential to revolutionize the research in drug delivery and provide the new generation of targeted cancer therapy.

12. Conclusion

γH2AX is a sensitive and dependable biomarker of DNA double-strand breaks, with important potential in the interface of molecular oncology and drug delivery technology. Its gradual onset during oral possibly malignant diseases up to oral squamous cell carcinoma illustrates its usefulness in identifying the presence of genomic imbalance and the disease progression. In addition to its diagnostic value, γH2AX has also been found to be an important pharmacodynamic biomarker in assessing the presence of DNA damage caused by treatment and is, therefore, especially useful in determining the effectiveness of chemotherapeutic agents, radiotherapy, and targeted therapies. In the framework of pharmaceutics, γH2AX is an endpoint that can be quantified to measure the efficacy of new drug delivery systems, such as nanocarriers, controlled release formulations, and targeted therapeutic platforms. The effective reflection of real-time cellular responses to the exposure to drugs allows it to optimize dosing regimens and increases accuracy in the treatment planning. In addition, the combination of γH2AX with molecular pathways including ATM -ATR signaling and DNA repair pathways enhances the design of pathway-based drug delivery strategies. Despite the persistent issues with the standardization and clinical validation, the integration of γH2AX into the research of drug delivery has a great potential of enhancing the treatment outcomes. All in all, γH2AX can be utilized as a useful tool to fulfill the goals of precision pharmaceutics and the next generation of targeted therapies in the management of oral cancer.

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