Biological dose monitoring in radiology using fluorescence microscopic determination of x-ray induced DNA double-strand breaks - a review

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Authors: M. Brand, C. Engert, M. Uder, M. A. Kuefner; Erlangen/DE
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Learning Objectives

To understand principle of biological dose monitoring using #H2AX immunofluorescence microscopy and to learn about x-ray induced DNA damages in radiology.
Background

Shortly after the discovery of X-rays their damaging effect on biological tissues was observed. For the determination of radiation exposure in diagnostic and interventional radiology usually physical or mathematical procedures are in use. Nowadays, there is evidence that the biological radiation damage depends not only on the dose but also on other individual factors that cannot be adequately covered by the established methods for dose measurement. A novel immunofluorescence microscopic approach, that is much more sensitive than previous biological methods, allows for the determination of distinct DNA double-strand breaks (DSB) in peripheral blood lymphocytes and thus renders an accurate estimation of the biological dose in diagnostic and interventional radiologic procedures.
Imaging Findings OR Procedure Details

#-H2AX Immunofluorescence Microscopy:

After the induction of DNA DSB the phosphorylation of the histone variant H2AX is one of the earliest cellular responses. This phosphorylated histones (termed #-H2AX) can be visualized by fluorescence microscopy as distinct fluorescent foci using specific primary and fluorescent secondary antibodies (Fig. 1) [1].

Using gradient centrifugation human lymphocytes can be isolated from blood samples. DNA DSB can be quantified with the #-H2AX immunofluorescence microscopic technique. The number of radiation-induced DSB is calculated by subtracting the pre-exposure control values from those values obtained after exposure. These determined x-ray induced DSB levels correlate well with the dose deposited [1]. In comparison to previous biological dosimetry approaches, this method is so sensitive that it can be used in dose range of diagnostic and interventional radiologic procedures.

DSB after CT:

In a first work, the DNA DSB have been studied in patients undergoing chest and / or abdominal CT scan. A clear increase of DSB was seen 30 minutes after CT, then the DSB values decreased rapidly due to repair processes and after 24 hours the pre-exposure levels were almost achieved (Fig. 2). The number of CT-induced DSB correlated very well with the dose length product (R2 = 0.9626) [1] (DSB induction after CT and correlation with the dose was also confirmed in another study [2]). Interestingly, at a comparable dose length products there was an excessive increase of the CT-induced DSB in one patient compared to the rest of the study collective (HOM-85 of Figure 2). In the past this patient had responded to radiation therapy with very severe side effects, and later a DNA repair defect, that was responsible for the high DNA DSB values, could be diagnosed [1]. This example shows that the individual radiation damage depends not only on dose but also on individual factors such as the repair capacity.

DSB after Cardiac CT:

In the recent years advances in CT technology have also meant that manufacturers of CT scanners offer more dose-efficient scanning procedures and protocols. This is particularly important in coronary CT angiography, where conventional helical scans lead to a rather high dose. ECG-triggered sequential scan modes (termed "step-and-shoot" technique) or a spiral scan with a very high pitch of about 3 or more ("Flash-CT") allows for the scanning of the entire heart in split of a second, and therefore should lead to a dose reduction. Two studies have demonstrated that these technologies cannot only reduce the calculated dose but also the DNA damage up to a factor of 10. In addition, individual scan parameters
had also an impact on CT induced DSB. In scans using 100-kV protocols the radiation
damage was significant lower than at 120 kV. CT-induced DSB also correlated very well
with the dose length product (Fig. 4) [4, 5].

**DSB and Iodinated Contrast Medium:**

Another factor is the individual i.v. application of iodinated contrast medium. In vitro
experiments have shown that at the same radiation dose significantly more DNA DSB
were measured in samples containing contrast medium (CM) compared to those without
contrast medium or after incubation with various control substances. The addition of
contrast medium immediately after irradiation of the samples had no effect on the number
of x-ray induced DSB, which suggests that the effect can be explained by an increased
DSB induction and not by decreased repair. In the same study, these results were
confirmed in vivo in patients who have been examined by chest CT. At a comparable
dose the radiation damage for contrast-enhanced CT scans were about a third higher
than for native studies (Fig. 3). As a cause for the increased induction of DSB in the
presence of contrast medium a greater photoelectric absorption in the iodine atoms of
the CM and the consecutive exposure of neighboring lymphocytes are assumed [3].

**DSB after Angiography:**

Angiography is an interesting field for biological dose estimation because the exposure
conditions differ considerably from other radiological procedures such as CT scans. The
X-rays are not applied during a single brief period, but fractionatedly over a longer period.
In patients who were treated by percutaneous transluminal angioplasty, a dependence
between the DSB-induction and the dose area product was found [6]. After cardiac
catheterization in children there is also an increase of DSB but the in vivo biological
dose was not linear within this low dose range, a result that has not been confirmed yet
[7]. Two other studies showed that the radiation-induced DSB correlated not well with
the dose area product in the entire collective of patients, but the separate analysis of
the various exposed body regions showed very good correlation coefficients (e.g., \( r = 0.71 \) for pelvic/leg angiographies, \( r = 0.96 \) for abdominal angiographies). Normalization
of the DSB levels to the individual dose area product showed significant differences for
individual anatomic regions. The damage level during cardiac catheterization was the
highest, followed by abdominal intervention, angiography of the pelvis and leg and the
cerebrum. These differences can be explained by the different blood volumes in the
various body regions and the associated variable number of exposed lymphocytes [8, 9].

**Estimation of DSB in Tissue:**

The dependence on exposed blood volume shows the limitations of \( \gamma \)-H2AX
immunfluorescence microscopy. The method reaches its limits especially in radiation
exposure of body regions with low blood volumes like the female breast. Nevertheless,
in a cohort of patients undergoing mammography, a very slight but significant increases of DSB (p = 0.0004) was measured in blood lymphocytes. However, these values underestimate the radiation damage in exposed tissues due to the mixing with non exposed blood but an estimation of the DNA damage in tissues is possible by using cells, exposed in biological (e.g. porcine breast) or in artificial phantoms (e.g. Alderson phantom) [unpublished data].
Fig. 1: Principle of visualization of DNA DSB

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Fig. 2: DSB induction and repair after CT of the chest and/or abdomen


Fig. 3: Influence of iodinated contrast medium on radiation-induced DSB


Fig. 4: DSB after cardiac CT: correlation with the DLP and the influence of tube voltage

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Conclusion

Using #-H2AX immunofluorescence microscopy it is possible to estimate radiation-induced DNA DSB in the dose range of diagnostic and interventional radiologic procedures. The DSB induction correlates well with the dose deposed and the influence of individual factors (e.g. DSB repair capacity, application of iodinated contrast medium etc.) can be considered. The radiation damage depends also on individual scan parameters / protocols (e.g. tube voltage) and new technologies (e.g. "Flash-CT") can lead to a reduction of the DSB-induction. Finally, using biological phantom models allow for estimation of the local radiation damage in exposed tissues.
Personal Information

Dr. Michael A. Kuefner
University of Erlangen
Department of Radiology
Maximiliansplatz 1
91054 Erlangen, GERMANY
michael.kuefner@uk-erlangen.de

Dr. Michael Brand
University of Erlangen
Department of Radiology
Maximiliansplatz 1
91054 Erlangen, GERMANY
michael.brand@uk-erlangen.de

Christina Engert
University of Erlangen
Department of Radiology
Maximiliansplatz 1
91054 Erlangen, GERMANY

Matthias Sommer
University of Erlangen
Department of Radiology
Maximiliansplatz 1
91054 Erlangen, GERMANY
References


