Editorial

Plasma levels of serum amyloid A1 and mortality after exposure to high-dose radiation

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Presented in *Annals of Translational Medicine*, Jinfeng Huang and colleagues' study (1) of the association between tissue/plasma levels of the serum amyloid A1 (SAA1) protein and dose of acute ionizing radiation exposure, highlights the potential benefits of SAA1 monitoring for triage purposes during potential mass-casualty events of exposure of humans to unknown doses of ionizing radiation. Two relatively separate potential utilities of measuring SAA1 in high-dose radiation exposed humans are proposed and discussed by the authors: one is reconstruction of exposure dose and second is prediction of adverse health outcome.

Scenarios of potential undesired human exposure to high doses of ionizing radiation (>1 Gy) include nuclear power plant accidents, such as Chernobyl and Fukushima (2), dirty bomb terrorist attacks (3) and military activities and warfare using nuclear weapons (4). Although the scenarios of nuclear power plant accidents have been of primary concern for decades, the terrorist and military nuclear events have gained attention due to the recent political insurgencies worldwide and, most recently, alleged changes in the US and Russia's national military postures implying the use of tactical nuclear weapons in regional conflicts (5). It is important to note that undesired exposures of humans to high-dose radiation are extremely rare. Even during nuclear accidents, the vast majority of exposed individuals receive low to moderate doses of radiation that do not cause life threatening acute disease. Nonetheless, identifying high-dose exposed individuals in a timely fashion would save lives; therefore, preparedness for triage of irradiated human cohorts is an important issue.

Such triage would involve medical surveillance and various tests to reconstruct radiation exposure dose to segregate exposed groups for prioritization of remediation and treatment (6,7). Dose reconstruction using biological end-points is collectively referred to as biodosimetry. Currently, the "golden standard" for human biodosimetry is the assessment of the frequency of dicentric chromosome aberrations in peripheral blood lymphocytes or the dicentric chromosome assay (DCA) (8). This analysis is however prone to large variability due to several factors, such as the need for laboratory manipulations to mitotically stimulate lymphocytes and thus producing variable outcomes or human subjectivity in scoring dicentric chromosome aberrations. Therefore, in order to maintain emergency preparedness, countries maintain their national biodosimetry facilities and capabilities and regularly perform emergency exercises, as wells as intercomparison studies involving multiple countries and aiming at standardization of the DCA (9,10). Although various automation and optimization solutions for performing the DCA have been proposed (11,12), no consensus exist and the assay is still widely considered a labor-intensive and time-consuming

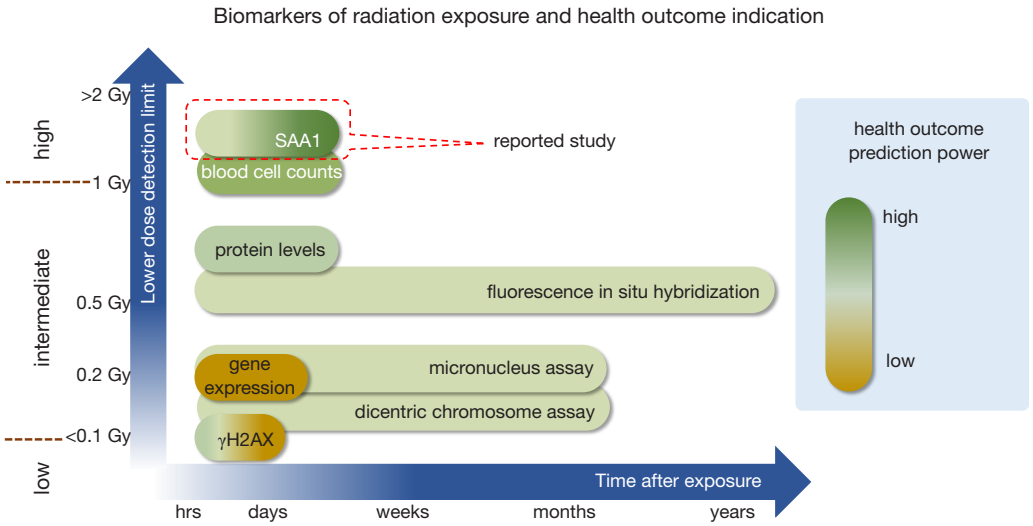

Figure 1 A diagram showing a relationship between the lower dose detection limit, the applicability time period after exposure and the health outcome prediction power for several biomarkers/assays for potential use in biodosimetry and health management upon accidental exposure of humans to unknown doses of ionizing radiation. The results by Huang *et al.* (1) (red dashed selection) are strongly relevant to the ability to predict adverse health outcome.

technique presenting a bottleneck for an adequate response to a potential mass-casualty event. Alternative methods for reconstructing unknown radiation dose have been explored (13), including those based on a widely known marker of DNA double-strand breaks γH2AX (14), gene expression changes (14) and several other biomarkers of exposure to radiation. High-throughput automation have also been proposed for non-dicentric based methods (15).

The idea of measuring blood plasma levels of various proteins for biodosimetry and triage is an attractive alternative to the DCA since results can be obtained much faster. Also, this work does not involve sophisticated microscopy analyses and is adaptable for high-throughput automation. Sure enough, such studies have been carried out previously, however blood plasma proteins turned out to be of limited use at lower doses. Indeed, the lower dose detection limit of the DCA of 0.2 Gy could not be reached using blood plasma proteins (16,17) (*Figure 1*). It is not surprising then that Huang *et al.* could only see SAA1 increases in the plasma of mice exposed to doses of ≥2 Gy, suggesting that it can be used for exclusively high-dose exposed individuals and should be combined with other more sensitive techniques. Arguably, this represents a limitation of the utility of SAA1 as a biomarker of exposure dose since, as was mentioned before, majority of exposed people upon mass-casualty nuclear accidents would be exposed to low doses.

Why the choice of the authors fell onto the SAA1 protein? It is a member of a small family of serum amyloid A proteins (SAA). SAA1 constitutes about 70% of acute-phase SAA response to proinflammatory stimuli (18) and has been implicated in a wide range of human pathologies, including respiratory disease, and it was proposed as a prognostic marker (19). Since acute radiation syndrome upon high-dose exposure is accompanied by acute systemic inflammation, the choice of Huang *et al.* to examine the link of SAA1 with acute radiation exposure outcomes was logical and well justified. Indeed, SAA has previously been implicated in acute radiation toxicity and proposed, in combination with other protein markers and blood cell counts, as a biomarker of exposure (17,20). Several aspects pursued by Huang *et al.* in their study allowed the authors to generate important novel knowledge.

Firstly, they examined the plasma levels of SAA1 in the extended period of time post-irradiation, which resulted in a very interesting bi-phasic kinetics of SAA1 increases. The initial peak between 6–24 h disappeared and reappeared at >5 days post-exposure in high-dose exposed mice only. One potential implication of this discovery is the possibility to perform this assay days after exposure of humans, when earlier screening could not be done, to identify severely injured victims.

Second important observation was that SAA1 levels responded not only to total-body irradiation, but also to various partial-body irradiation modes that either included or excluded the liver, a major producer of systemic SAA1. Upon real-life exposure scenarios, it is anticipated that various body parts of humans may be exposed to radiation differently. The ability of the plasma SAA1 levels to respond to partial body exposures suggests its utility for such complex exposure patterns. However, it is important to note that under such circumstances, the SAA1 plasma level would rather serve as a biomarker of health effect, but not exposure dose.

Last, and arguably most important result of the study, is the revealed correlation between the second peak of SAA1 and the mortality of the exposed mice. Huang and colleagues are to be applauded for noticing and exploring in detail the inverse correlation between the SAA1 levels at 5 and 7 days post-exposure and the survivability of animals. They carried out an additional experiment in which they monitored SAA1 levels longitudinally in 10 Gy exposed mice and, using individual mouse data, estimated specificity, sensitivity and precision of predicting lethality by measured SAA1 levels. They show that using a cut-off value of 1.15 μg/mL of SAA1 on day 7 post-exposure, a specificity of 2/3, sensitivity of 13/16 and precision of 13/14 could be achieved for predicting a lethal outcome. The authors further validate their result by protecting lethally irradiated mice with a radioprotecting drug amifostine and demonstrating that such protection was accompanied by the reduction of SAA1 plasma levels when compared to the radiation only group. Curiously, a month after the publication by Huang *et al.*, an independent report was published showing that in mice rescued from the acute radiation syndrome by a drug captopril, the improvement correlated with reduced plasma levels of SAA1 (21), consistent with the major observation of the study by Huang and colleagues.

Can these results obtained in mice be extrapolated to humans? Inability to reproduce effects observed in preclinical studies in humans is a well appreciated issue in translational biomedical research (22-24). Unfortunately, biodosimetry research area may also be flawed by inappropriate mouse-to-human extrapolation. Thus, it was shown that many radiation-responsive genes changed in opposite directionalities in human and mouse cells (25). To this end, the final piece of data presented by Huang and colleagues is very important. They validated their mouse results in a cohort of human nasopharyngeal carcinoma patients, showing that blood plasma SAA1 concentration increased after local irradiation of the diseased tissue at 60–70 Gy.

To truly improve the knowledge on the SAA1 utility for biomonitoring victims of radiological accidents, further research will require a large human patient cohort size, more mechanistic data relating SAA1 response to specific pathological conditions, and validation of the results for mixed radiation exposure, e.g., gamma-radiation + neutrons, that are typical for real-life scenarios. This reported study nonetheless represents an important step forward in managing severe acute radiation syndrome in accidentally exposed human cohorts.

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Footnote

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm.2020.03.172). The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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