Radiation Survivors: Understanding and Exploiting the Phenotype following Fractionated Radiation Therapy

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Abstract

Radiation oncology modalities such as intensity-modulated and image-guided radiation therapy can reduce the high dose to normal tissue and deliver a heterogeneous dose to tumors, focusing on areas deemed at highest risk for tumor persistence. Clinical radiation oncology produces daily doses ranging from 1 to 20 Gy, with tissues being exposed to 30 or more daily fractions. Hypothesizing the cells that survive fractionated radiation therapy have a substantially different phenotype than the untreated cells, which might be exploitable for targeting with molecular therapeutics or immunotherapy, three prostate cancer cell lines (PC3, DU145, and LNCaP) and normal endothelial cells were studied to understand the biology of differential effects of multifraction (MF) radiation of 0.5, 1, and/or 2 Gy fraction to 10 Gy total dose, and a single dose of 5 and 10 Gy. The resulting changes in mRNA, miRNA, and phosphoproteome were analyzed. Significant differences were observed in the MF radiation exposures including those from the 0.5 Gy MF that produces little cell killing. As expected, p53 function played a major role in response. Pathways modified by MF include immune response, DNA damage, cell-cycle arrest, TGF-β, survival, and apoptotic signal transduction. The radiation-induced stress response will set forth a unique platform for exploiting the effects of radiation therapy as “focused biology” for cancer treatment in conjunction with molecular targeted or immunologically directed therapy. Given that more normal tissue is treated, albeit to lower doses with these newer techniques, the response of the normal tissue may also influence long-term treatment outcome. Mol Cancer Res; 11(1); 1–8. ©2012 AACR.

Introduction

The biologic consequences of radiation exposure are of interest for cancer etiology and treatment. The potential negative consequences of ionizing radiation have been recently highlighted through reports of treatment errors in radiation therapy (RT; ref. 1), risk from computed tomography scans (2), and radionuclide release from the Fukushima Nuclear Power Plant disaster (3, 4). On the positive side, the impact of the MF lower dose on the increased volume of irradiated normal tissue remains to be elucidated.

On the basis of our group’s interest in understanding the cellular response to radiation-induced stress, we put forward and tested a hypothesis that the molecular response of cells to single-dose (SD) radiation would be different from the response to MF radiation; and that the cells that survived MF would become more alike by virtue of their adaptation to radiation (6). This review comprises of analyses of the findings from our laboratory (7–9) and published reports by others groups (6, 10–14) on effects of SD and MF on cellular response. There are several translational goals that need to be considered which include:

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Understanding the molecular characteristics of tumor cells that survive fractionated radiation and the impact of genetic background on MF-induced changes.

What is the impact of the size of the dose per fraction (including low doses that might occur at the tumor periphery and in the surrounding normal tissue)?

As molecular-targeted drugs require the presence and persistence of a target, can MF be used to induce such targets rather than depend on its presence and, therefore, make molecular-targeted therapy more effective and broadly applicable?

Is there a preferred "omics" approach or combination of methods (mRNA, miRNA, or phosphoproteomics) with which to assess these changes?

**Dose-heterogeneity in clinical radiation therapy**

In the clinic, MF radiation is used because of its normal tissue sparing effects (15) with the maximum radiation dose delivered based on normal tissue tolerance from clinical experience (16). The less complicated RT modalities including opposed pairs, 4-field configuration and, to some extent, 3-dimensional conformal RT use a limited number of fields with a relatively uniform energy deposition across the beam and a homogeneous dose within the tumor. In contrast, new technological approaches such as intensity-modulated radiation therapy (IMRT; ref. 17), image-guided radiation therapy (IGRT; ref. 17), and heavy ion therapy (protons and carbon; ref. 18) are designed to reduce the high doses delivered to normal tissues. IMRT and IGRT use dose painting and sculpting to deliver radiation within the target so that dose is often not homogenous within a tumor. A specified target may receive a higher dose based on local tumor burden, the presence of a physiologic area at risk for local failure (such as hypoxia) or persistence of an imaging abnormality [such as positron emission tomography (PET)] (19). IMRT and IGRT use multiple and often noncoplanar intensity-modulated beams such that there is more normal tissue treated to some moderate dose. Thus, there are more tissues treated with increased dose heterogeneity. Recently, the advances in diagnostic imaging, the ability to stay on target during radiation treatment by accounting for patient and tumor intrafraction motion, and an interest in shortening treatment time for biologic (prostate cancer) and/or patient convenience (breast cancer) have also led to the use of larger doses per fraction (i.e., hypofractionation). Thus, in current clinical RT, tissues are exposed to MF radiation in a range of doses for 1 to 7 weeks.

Figure 1 provides an example of dose heterogeneity in clinical radiation oncology. The IMRT plan is for a pharyngeal tumor, which by design covers the tumor well, but also has significant dose distribution to the nearby normal tissue with the majority of the tissue behind the vertebral region receiving more than 100 cGy/day as a result of multiple field configurations. The daily treatment dose is heterogeneous including a maximum dose of almost 230 cGy/day with much of the tissue receiving as much as 150 cGy/day, and other regions receiving between 50 and 150 cGy/day.

**Molecular phenotype depends on fractionation, fraction size, and underlying genetic profile**

In RT, the multiplicity of doses to which patients are exposed may engage different biologic processes and molecular pathways. The daily dose ranges include high doses from...
ablative hypofractionation that are more than 10 Gy (often close to 15–20 Gy; refs. 20, 21), moderate dose of 1 to 10 Gy (22), low doses including treatments designed to take advantage of low-dose hypersensitivity approximately 0.5 Gy (23). [Note: There are lower doses (~10 cGy) that elicit low dose “adaptive” responses such as the nontargeted/bystander effects in unirradiated cells (24) discussed below]. Differences in the effects of fractionated and SD radiation including those from our laboratory have been previously documented (6–7, 10–12) and include the induction of stress-response (7, 12) and immune-related (6–7, 10–11) genes by fractionated radiation.

In studies comparing MF and SD from our laboratory, Tsai and colleagues showed significant differences in the gene expression profiles following MF and SD, with MF uniquely upregulating interferon-related genes and TGF-β associated genes in a prostate cancer xenograft model and in vitro in prostate, breast, and gliosarcoma cells lines (6). Our analyses of the global gene profiles following radiation (MF and SD) show a more robust MF-induced gene expression in Human Coronary Artery Endothelial Cells (HCAEC; in preparation), LNCaP (9), and PC3 (7) in comparison to SD. The observed gene expression patterns have shown MF radiation to be more immune-modulatory in comparison with SD in LNCaP (9) PC3 (7) and normal HCAEC (in preparation) but not in DU145 cells (7). Figure 2 serves as a representative illustration, highlighting the differences between single and fractionated radiation by depicting differences in expression of immune response gene using SD 10 Gy and MF 1 Gy x 10. It also illustrates that there is an inflection point after 6 to 7 fractions in MF. In comparison to SD, the majority of gene and miRNA changes were also more robust and stable up to 72 hours after the end of MF (7), suggesting a sufficiently stable phenotype that might affect tissue/tumor response and also potentially be targetable with drug therapy (7).

Dewan and colleagues showed an MF-induced immune-mediated abscopal response with anti-CTLA-4 antibody, in breast and colon cancer xenograft experimental models. The same abscopal response was not observed with SD; in comparison with SD, MF dramatically improved the local and secondary tumor control (10). More recently, following MF, Postow and colleagues observed immune activation and elevated antibody levels against a NY-ESO-1 (a cancer

Figure 2. Adaptation takes time. A, heat maps depicting the expression patterns of immune response genes 24 hours following exposure to 10 Gy as SD or 10 fractions of 1 Gy (MF) in LNCaP, PC3, and DU145. B, inflection point. Samples were collected 24 hours after the indicated number of 1 Gy radiation fractions in PC3 and DU145. For MF, there was at least a 6-hour window between each fraction; samples were collected 24 hours after final fraction. Data represent fold change in IFI44 expression determined by reverse transcriptase PCR. Data were adapted in part from ref. 7.
<table>
<thead>
<tr>
<th>Cell type</th>
<th>Radiation protocol</th>
<th>Functional categories</th>
<th>Type of analysis</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCF-7</td>
<td>MF 2Gy ×20</td>
<td>Growth regulator, apoptosis, DNA repair, DNA replication, cell adhesion, angiogenesis, regulator, cell division, growth factor, cytokine</td>
<td>In vitro, mRNA</td>
<td>Li and colleagues (2001; ref. 12)</td>
</tr>
<tr>
<td>MCF-IR20</td>
<td>Cell division, apoptosis, GTPase regulator, growth factor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCF-7</td>
<td>MF 2Gy ×5</td>
<td>Apoptosis, cell senescence, cell-cycle control, DNA damage repair, angiogenesis, signal transduction, and transcription factors, angiogenesis</td>
<td>In vitro, mRNA</td>
<td>Madhusoodhan and colleagues (2009; ref. 51)</td>
</tr>
<tr>
<td>SD 10Gy ×1</td>
<td>Apoptosis, cell senescence, cell-cycle control, DNA damage repair, angiogenesis, signal transduction and transcription factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCF-7</td>
<td>MF 2Gy ×5</td>
<td>Cell-to-cell signaling and interaction; DNA replication, recombination, and repair; nucleic acid metabolism</td>
<td>In vitro, mRNA</td>
<td>Tsai and colleagues (2007; ref. 6)</td>
</tr>
<tr>
<td>SF539</td>
<td>MF 2Gy ×5</td>
<td>Cancer, infectious disease, respiratory disease, cellular development, cellular growth and proliferation, connective tissue development and function</td>
<td></td>
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</tr>
<tr>
<td>DU145</td>
<td>MF 2Gy ×5</td>
<td>Cancer, infectious disease, respiratory disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCF-7, SF539, DU145</td>
<td>SD 10Gy ×1</td>
<td>Cancer, infectious disease, respiratory disease, molecular transport, hematological disease, hereditary disorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DU145</td>
<td>MF 1Gy ×5</td>
<td>Cell-to-cell signaling and interaction, drug metabolism, lipid metabolism</td>
<td>In vivo, mRNA</td>
<td></td>
</tr>
<tr>
<td>LNCaP</td>
<td>MF 1Gy ×10</td>
<td>Organismal survival, cancer, cell death, molecular transport, drug metabolism, small molecule biochemistry, inflammatory response, cellular development, cellular growth and proliferation, cancer, reproductive system disease, endocrine system disorders</td>
<td></td>
<td>Simone and colleagues (ref. 9)</td>
</tr>
<tr>
<td>SD 10Gy ×1</td>
<td>Organismal survival, cancer, cell death, molecular transport, drug metabolism, small molecule biochemistry, inflammatory response, cellular development, cellular growth and proliferation, cancer, reproductive system disease, endocrine system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PC3</td>
<td>MF 1Gy ×10</td>
<td>Cell cycle, DNA binding, proliferation, response to stress, transcription factor, signal transduction, DNA replication, histone, cyclin, immune response</td>
<td>In vitro, mRNA</td>
<td>John-Aryankalayil and colleagues (2010; ref. 7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cell cycle, gastrointestinal disease, hepatic system disease, hematological system development and function, hematopoiesis, tissue development</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cell cycle, DNA binding, DNA replication, response to stress, DNA repair, proliferation, transcription factor, signal transduction, cyclin, histone</td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Immune response, DNA binding, response to stress, interferon, signal transduction, proliferation, apoptosis, transcription factor, ubiquitin, inflammatory response</td>
<td>In vitro, mRNA</td>
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(Continued on the following page)
The role of miRNAs in radiation and cytotoxic stress response is becoming increasingly clear (31, 32). They are key regulators of gene expression by posttranscriptional interference of mRNAs and function as oncogenes (miR-17-92 cluster, miR21, miR106b-93-25 cluster, miR-155, miR221, and miR-222), tumor suppressor (let-7, miR-15-16 cluster, miR-34, and miR203) and epigenetic modulators. Mounting evidence associating miRNAs and epigenetics show some miRNAs to be epigenetically regulated (let-7, miR-34 family, miR-124, miR-148, miR-203, and miR-200 family; refs. 33, 34), whereas some have been reported to repress epigenetic drivers by directly targeting key genes such as DNA methyl transferases, histone deacetylases and histones (miR-26, miR-29, miR-101, antigen expressed in 30%–40% of melanomas) in a melanoma patient treated with anti-CTLA-4 antibody, ipilimumab (14). Clinical trials combining fractionated radiation and ipilimumab are currently underway in stage IV melanomas (ClinicalTrials.gov number, NCT01449279; ref. 25) and advanced prostate cancer (ClinicalTrials.gov number, NCT00861614).

As much as radiation dose, quality, dose rate, and fractionation (10) all play an important role in cellular response to radiation, observed differences in the response to SD and MF radiation regimens are also dependent on the underlying genetic profiles. Following radiation (MF and SD), our studies have shown 2,255 differential expressed genes in HCAEC (in preparation), 978 in LNCaP (9), 343 in PC3 and 116 in DU145 (7). The genes most altered by both radiation protocols were also different between the three prostate cancer cell lines (7, 9). A list of top 10 upregulated and 10 downregulated genes in the 3 prostate cancer cell lines are provided as Supplementary Information. As previously stated, MF altered more genes than SD in HCAEC (normal endothelial cell), LNCaP (p53-wildtype), and PC3 (p53-null). In contrast, SD altered more genes in DU145 (p53-mutant). p53, a vital tumor suppressor, is associated with activation of DNA repair, apoptosis, and radiosensitivity. The diverse p53 status of these cells likely plays a central role in their radiation response and could provide a partial explanation as to why different pathways were top ranked in their radiation response and could provide a partial explanation as to why different pathways were top ranked in their radiation response.

In vitro
dna binding, response to stress, immune response, cell cycle, transcription factor, proliferation, histone, ubiquitin, transcription factor, interferon

Table 1. Differences in gene profiles between SD and MF radiation (Cont’d)

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Radiation protocol</th>
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</tr>
</thead>
<tbody>
<tr>
<td>SD 10Gy x1</td>
<td>DNA binding, signal transduction, immune response, cell cycle, response to stress, proliferation, histone, ubiquitin, transcription factor, interferon</td>
<td>In vitro, mRNA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DU145 MF 1Gy x10</td>
<td>DNA binding, response to stress, apoptosis, proliferation, signal transduction, immune response, interferon, DNA damage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD 10Gy x1</td>
<td>DNA binding, response to stress, immune response, cell cycle, transcription factor, proliferation, protease, histone, interferon, cyclin</td>
<td>In vitro, mRNA</td>
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<td></td>
</tr>
</tbody>
</table>

NOTE: Table summarizes pathway analysis of previously reported gene, following exposure to SD and MF radiation.
miR-148, mir-203, miR-205, miR-214, and miR-449; refs. 30, 33, 34). Their dysregulation has been implicated in multiple cancers; the radiation-induced differential expression of miRNA is also well documented (31, 35, 36). Mueller and colleagues report that a family of miRNAs (miR-99 family) is upregulated in response to radiation (2Gy/C2) and reduces the efficiency of DNA repair in two p53þ breast (MCF7) and prostate (LNCaP) cancer cell lines. They further showed decreased DNA repair efficiency with mir-99 expression following MF (13). miR-99 expression has also been reported to be decreased in advanced and more radioresistant cancers (13, 37). This finding supports earlier reports from our group; we show increased expression of select miRNA after radiation exposure, especially MF in LNCaP and PC3 (Table 2; ref. 8). Furthermore, we showed increased miR-99 expression following MF in PC3 but not in LNCaP. In contrast, let-7, which is also typically underexpressed in cancers and associated with poor prognosis in patients (38), was upregulated after MF in LNCaP and PC3 (8). Let-7, a tumor suppressor miRNA, regulates cellular proliferation and expression of oncopgenes such as RAS/c-MYC and HMGA-2; its overexpression has been reported to inhibit tumor development and growth (38–40).

miRNAs are crucial to the maintenance of radiation-induced response and although, miRNA profiling is a promising diagnostic tool, as expression levels of specific miRNA have been associated with major cancer outcomes, it should be noted that the baseline miRNA expression levels in different cancers are not always predictive of response (8, 13) so that postexposure analysis will be informative in addition to baseline assessment. Further studies are necessary to assess the role of epigenetics and p53 function in radiation-induced miRNA response and to understand the how miRNAs contribute to the maintenance of MF-induced adaptation, as cells pass on their "survivor" phenotype to subsequent generations.

### Tumor heterogeneity

Inter- and intratumoral heterogeneity is a feature of carcinogenesis and tumor progression including malignant transformation, metastasis, immune evasion, and treatment resistance. Gerlinger and colleagues recently mapped the heterogeneity in four renal cancer patient samples and the associated metastases using exome sequencing. They report multiple genetic and functional mutations within a single tumor for mTOR (41) and its downstream targets. Recent reports have also highlighted the heterogeneity within different tumors (42–44). This has implications for biomarkers, diagnostics, therapeutic efficacy, and relatively specific molecular-targeted therapies (41–44). We are interested in exploring the effect of radiation on tumor heterogeneity,

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<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>LNCaP</td>
<td>MF 0.5Gy × 10</td>
<td>Genetic disorder, skeletal and muscular disorders, inflammatory disease</td>
<td>In vitro, miRNA</td>
<td>John–Aryankalayil et al. (2012; ref. 12)</td>
</tr>
<tr>
<td></td>
<td>1Gy × 10</td>
<td>Reproductive system disease, genetic disorder, skeletal and muscular disorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>SD 5Gy × 1</td>
<td>Cell cycle, cellular growth and proliferation, cellular development</td>
<td>In vitro, miRNA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10Gy × 1</td>
<td>Cellular development, cellular growth and proliferation, cell cycle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PC3</td>
<td>MF 0.5Gy × 10</td>
<td>Cell death, liver necrosis/cell death, cell cycle</td>
<td>In vitro, miRNA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1Gy × 10</td>
<td>Reproductive system disease, genetic disorder, skeletal and muscular disorders</td>
<td></td>
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<tr>
<td></td>
<td>SD 5Gy × 1</td>
<td>Cellular development, embryonic development, nervous system development and function</td>
<td>In vitro, miRNA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10Gy × 1</td>
<td>Cellular assembly and organization, cell death, skeletal and muscular system development and function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DU145</td>
<td>MF 0.5Gy × 10</td>
<td>Cell cycle, cell death, cell morphology</td>
<td>In vitro, miRNA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1Gy × 10</td>
<td>DNA replication, recombination and repair, cell death, liver necrosis/cell death, inflammatory response, antigen presentation, cell-to-cell signaling and interaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>SD 5Gy × 1</td>
<td>None</td>
<td>In vitro, miRNA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10Gy × 1</td>
<td>Cell cycle, cell death, cell morphology</td>
<td></td>
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</table>

**NOTE:** Table summarizes pathway analysis of previously reported microRNAs, following exposure to SD and MF radiation.
particularly how the adaptation to MF could be exploited to therapeutic advantage.

The new perspective for radiation oncology

The novel observation from these studies is that changes in the molecular characteristics of the surviving tumor cells and normal tissues after MF may affect treatment outcome and could potentially be exploited. IMRT and IGRT techniques create a heterogeneous dose distribution within the tumor; hypofractionation uses large doses in either a single or a limited number of fractions. While physical techniques allow for 2 beneficial outcomes: (i) increasing the dose to regions of interest within the tumor volume and (ii) decreasing the maximal normal tissue dose near the tumor, more tissue is exposed to some radiation, much of it receiving approximately half the daily tumor dose and some much lower. The normal tissue and stromal cells that receive repeated lower doses do respond and the impact of this on the tumor microenvironment remains to be elucidated. Our data show that there is a different molecular profile between tumor cell type and differences are dependent on radiation dose per fraction (Tables 1 and 2).

Mathematical models based on clinical experience are useful for treatment selection in the clinic (15, 38, 45) but these do not describe biologic processes that are changed. Our studies have shown that cells that survive and remain clonogenic after MF are phenotypically different from the starting cells. Furthermore, cells may be lethally irradiated in terms of clonogenic potential yet survive and could influence outcome, such as late effects (46, 47). Proteomics data being analyzed indicate that a specific molecular target (such as NF-kB and PARP) may go in opposite directions following SD and MF. Ongoing and future plans include in vivo studies, a broader range of tissue types and genetic background, effect of hypoxia, and usage of MF as part of combined modality treatment and immunotherapy (10).

How does this fit with the newer models for cancer treatment?

New models of molecular-targeted therapy targets both oncogene addiction and nononcogene addition (48); nononcogene addition could be potentially be produced using a specified course of MF radiation (7). Synthetic lethality takes advantage of the cell’s susceptibility due to a defective pathway (49, 50) and it might be possible to induce cell susceptibility using MF to replace the therapeutic dependence on mutated pathway, thereby broadening the potential for synthetically lethal drugs. The extensive heterogeneity within tumors (41–44) presents a challenge as to what targets can be effectively exploited, so that the cellular adaptation to radiation could generate a target and/or reduce heterogeneity. As noted above, baseline miRNA expression between various cell types is not always predictive of magnitude of response (8, 13) so that sampling a tumor after being challenged by radiation may provide a new approach to molecular targeting. We recognize that there is much to be done; however, there may be very innovative ways of using the ability to target radiation to generate changes that can improve treatment efficacy. It is a new paradigm of using radiation “pharmacokinetics and pharmacodynamics.”

In summary, understanding and using the radiation stress response and the adaptation to MF radiation for both tumors and normal tissues coupled with the advances in imaging and technological delivery of radiation provides potential for a unique targeting situation for combined modality therapy and immunotherapy, an approach we call “focused biology” (5).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors’ Contributions

Conception and design: A.Y. Makinde, M. John-Aryankalayil, N. Coleman
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): A.Y. Makinde, M. John-Aryankalayil, D. Cerna
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A.Y. Makinde, M. John-Aryankalayil, S.T. Palayoor, N. Coleman
Writing, review, and/or revision of the manuscript: A.Y. Makinde, M. John-Aryankalayil, D. Cerna, N. Coleman
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): A.Y. Makinde, M. John-Aryankalayil, N. Coleman
Study supervision: A.Y. Makinde, M. John-Aryankalayil, N. Coleman

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