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REVIEW

Activation of stem cell up-regulation/mobilization: a cardiovascular risk in both mice and humans with implications for liver disease, psoriasis and SLE

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Abstract: Experimentally induced injury triggers up-regulation and mobilization of stem cells in *Apoe -/-* mice that causes accelerated atherosclerosis. *Abca1 -/- Abcg1-/-* mice have chronic activation of stem cell up-regulation/mobilization and accelerated atherosclerosis. In addition, the *Abca1 -/- Abcg1-/-* mice have elevation of serum cytokines G-CSF, IL-17 and IL-23, each necessary for stem cell mobilization. IL-17 and IL-23 are elevated in two human illnesses that have cardiovascular (CV) risk independent of traditional risk factors—SLE and psoriasis. Serum G-CSF, which can be elevated in liver disease, predicts major adverse cardiovascular events in humans. These serum cytokine elevations suggest activation of the stem cell mobilization mechanism in humans that results, as in mice, in accelerated atherosclerosis. Efforts to reduce CV disease in these patient populations should include mitigation of the diseases that trigger stem cell mobilization. Since activation of the stem cell up-regulation/mobilization mechanism appears to accelerate human atherosclerosis, use of stem cells as therapy for arterial occlusive disease should distinguish between direct administration of stem cells and activation of the stem cell up-regulation/mobilization mechanism.

Keywords: stem cells, HDL, vascular disease, SLE, psoriasis, liver disease

Introduction

Experimentally induced injury (myocardial infarction (MI)) and stress trigger up-regulation and mobilization of stem cells in *Apoe -/-* mice. This process results in alterations in arterial plaques that accelerate atherosclerosis.[1,2] Stress in humans leads to the same changes as in mice, at least as far as could be practically studied; the work in mice included intravital microscopy in bone marrow and aortic root harvest.[2] While not proven experimentally, the concept that the stem cell up-regulation/mobilization mechanism also accelerates atherosclerosis in humans is supported by clinical observations.

Abca1 -/- Abcg1-/- mice (deficient in ATP-binding cassette transporters ABCA1 and ABCG1) have chronic stem cell mobilization, accelerated atherosclerosis and elevated serum levels of Interleukin-17 (IL-17), Interleukin-23 (IL-23) and Granulocyte colony-stimulating factor (G-CSF).[3–5] Antibody blocking of any of the three cytokines in *Abca1 -/- Abcg1-/-* mice reduces stem cells in peripheral circulation, indicating that at least in these mice each of the three cytokines are critical components in the stem cell mobilization process.[4] These cytokines likely serve similar roles in humans.

G-CSF is used clinically to up-regulate/mobilize stem cells for collection for bone marrow transplantation.[6] Serum G-CSF levels have been shown to predict major

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adverse cardiovascular events in humans, which parallels the association in mice.[7] Serum G-CSF can be elevated in liver disease,[8,9] with several liver diseases (NAFLD [non-alcoholic fatty liver disease], AFL [alcoholic fatty liver disease], and HCV [hepatitis C virus]-related disease) reportedly associated with premature atherosclerosis.[10] Elevated serum levels of IL-17 and IL-23 have been reported in two human illnesses that have cardiovascular (CV) risk independent of traditional risk factors, i.e., systemic lupus erythematosus and psoriasis.[11–16] The elevated serum levels of these cytokines suggest that the injuries due to these diseases have triggered the stem cell up-regulation/mobilization mechanism resulting in acceleration of atherosclerosis and thus the CV risk associated with these diseases.

Stem cells have been employed in efforts to treat arterial occlusive disease, both cardiac and peripheral.[17–19] Different methods of delivering stem cells to target sites have been employed, including direct administration of cells and activation of the stem cell up-regulation/mobilization process.[17,18] These methods may not be equivalent if activation of the stem cell up-regulation/mobilization mechanism causes accelerated atherosclerosis in humans.

Discussion

Evaluation of chronic stem cell up-regulation/mobilization as a CV risk in humans

Humans with ABCA1 deficiency would be logical targets for investigation, as we expect them to have similar conditions as the *Abca1 -/- Abcg1-/-* mice—namely, stem cell up-regulation/mobilization; elevated serum levels of G-CSF, IL-17 and IL-23; and accelerated atherosclerosis. Human deficiency of ABCA1 causes Tangier disease in homozygotes, and causes familial hypoalphalipoproteinemia in heterozygotes. These individuals may have an increased risk of atherosclerotic disease.[20] Unfortunately neither the number of stem cells in peripheral circulation nor the serum levels of IL-17, IL-23, or G-CSF have been reported in Tangier disease or familial hypoalphalipoproteinemia.

There are, however, other groups who have evidence for stem cell up-regulation/mobilization and who also have an increased incidence of atherosclerotic disease. Patients with systemic lupus erythematosus (SLE), psoriasis, and chronic liver disease have cytokine patterns suggesting activation of the stem cell up-regulation/mobilization mechanism. Both SLE[12,21] and psoriasis[14,22,23] are independent CV risk factors. The CV risk due to liver disease is less clear.[10,24,25]

Activation of stem cell up-regulation/mobilization in humans

Liver disease

The incorporation of bone-marrow-derived stem cells into adult tissues was originally described in the liver.[26] Following the discovery that adult bone-marrow-derived stem cells can become liver cells, researchers reported that bone-marrow-derived stem cells could be incorporated into other organs.[27,28] The same cytokines that are necessary for stem cell up-regulation/mobilization in *Abca1 -/- Abcg1-/-* mice can be elevated in human liver disease. Elevated serum G-CSF has been reported in diverse liver injuries, both acute and chronic. Lemoli et al. found that, following an injury to the liver (hepatic transplantation or resection), serum G-CSF increased significantly, as did the number of circulating stem cells.[29]

Stoiser et al. discovered that patients who had acute malaria with evidence of concurrent liver injury (elevated serum bilirubin and alanine transaminase (ALT)) also had significantly increased levels of G-CSF compared to healthy controls.[30] Kaya et al. compared patients with cirrhosis to normal controls, and found serum G-CSF levels significantly higher in the cirrhotic subjects.[9] All of the patients Kaya studied had hepatocellular carcinoma (HCC), which may produce G-CSF—a possible confounding variable in that study.[31] Bazarniy et al. studied patients with cirrhosis not known to have HCC, and also found serum G-CSF significantly higher than in a normal control group.[8] In addition to G-CSF, researchers have found elevated levels of cytokines IL-17 and IL-23 in cirrhotic patients.[9,32–34]

Serum G-CSF levels have been shown to be predictive of major adverse cardiovascular events independent of traditional cardiovascular risk factors.[7] The elevation of serum G-CSF in liver disease suggests that individuals with liver disease would have increased CV risk.

Cardiovascular Risk in Liver Disease

Cardiovascular risk is increased in some liver diseases and is not fully accounted for by traditional risk factors. Loria et al., reviewing literature on liver disease and cardiovascular risk, concluded,

> At variance with what [is] observed in the general population, patients with liver disease fail to display the strict and proportional association between increasing (total and LDL [low-density lipoprotein]) CH [cholesterol] and TG [triglyceride] levels and cardiovascular morbidity, suggesting that other factors … may be important.

They also noted that,

> Three common steatogenic liver diseases, NAFLD [non-alcoholic fatty liver disease], AFL [alcoholic fatty liver disease], and HCV [hepatitis C virus]-related disease are associated with premature atherosclerosis despite varying or even opposite lipid phenotypes.[10]

Puchner et al. used coronary CT angiography to investigate coronary artery plaque in patients with non-alcoholic fatty liver disease. Coronary plaque with high-risk features was more frequent in patients with NAFLD than those without NAFLD. The association between high-risk coronary plaque and NAFLD was independent of traditional risk factors.[24]

Tarantino et al., however, did not find serum Il-17 associated with atherosclerotic risk in the form of common carotid artery intima media thickness in NAFLD patients.[25] While arguing against a link between atherosclerotic risk and a cytokine associated with stem cell up-regulation/mobilization, the study had notable limitations including the diagnosis of NAFLD. Since the enrolled patients' liver enzymes were normal, the diagnosis of NAFLD was subjective, based on ultrasound (U/S) brightness of the liver.[25] U/S brightness, or echogenicity, unlike CT, has no units.[35]

In contrast, Puchner et al. used liver CT density measured in Hounsfield units for diagnosis.[24] An additional weakness was that Tarantino's patients had been on a low-fat diet (25% of calories) for three months prior to enrollment.[25] If these individuals had had NAFLD, the three-month diet might have reduced liver injury, and thus IL-17 levels.[36]

Liver disease alone provides limited support for activation of the human stem cell up-regulation/mobilization mechanism causing accelerated atherosclerosis, but the case is stronger when SLE and psoriasis are considered.

Systemic lupus erythematosus (SLE)

Individuals with SLE suffer chronic autoimmune multi-organ damage, which could trigger stem cell-mediated repair. As in patients with liver disease, patients with SLE can have elevated serum IL-17, IL-23, and G-CSF consistent with activation of up-regulation/mobilization of stem cells,[37–41] which could accelerate atherosclerosis.

Cardiovascular Risk in SLE

Cardiovascular risk is a well-recognized feature of SLE. Manzi et al. noted that, "Women with lupus in the 35- to 44-year age group were over 50 times more likely to have a myocardial infarction than were women of similar age in the Framingham Offspring Study".[42] Similarly, Jonsson et al. reported that the incidence of myocardial infarction in SLE patients was 9 times higher than in an age-matched control population.[43] In a review article, McMahon et al. reported that traditional cardiac risk factors could not fully account for the increased atherosclerosis risk seen in SLE patients.[21] Lupus duration and damage index score are both independent predictors of cardiovascular disease.[44] Lending support to the concept that SLE CV risk is independent of traditional risk factors, treatment of SLE patients with statin therapy did not clearly reduce CV risk.[45]

Researchers have found that at least some patients with SLE have elevated serum G-CSF, and that alone is predictive of elevated CV risk.[7,39] Other cytokines linked to stem cell mobilization are elevated in SLE. Chen XQ et al. reported that plasma IL-17 levels positively correlated with SLE disease activity index.[11] Wen et al. reported SLE patients to have serum IL-17 and IL-23 levels greater than normal, and that those levels decreased with SLE treatment.[16]

Cytokine levels in SLE are thus consistent with activation of the stem cell up-regulation/mobilization process. Confirmation in the form of detecting increased stem cells in circulation would be helpful, but unfortunately, investigation of stem cells in peripheral circulation in SLE has been limited. Moonen et al. did investigate levels of "circulating progenitor cells (CPCs) from bone marrow" in patients with SLE but with unfortunate timing. They did not find greater numbers of CPCs in SLE patients vs. healthy controls, but the SLE patients were all studied when their disease was inactive.[46]

Although an increase in circulating stem cells in SLE has not been documented, the CV risk is not thought to be due to the stem cells themselves, but rather to activation of the process that up-regulates and mobilizes them.[47] The pattern of serum cytokine elevations in SLE is consistent with activation of that process.

Patients with SLE provide clinical support for the concept that activation of the stem cell up-regulation/mobilization process results in accelerated atherosclerosis. Data on patients with psoriasis add additional support.

Psoriasis

Patients with psoriasis have both increased atherosclerotic risk and cytokine evidence of activation of the stem cell up-regulation/mobilization process. The timing of investigation

of cytokine levels vs. disease activity and injury would again be important, as in SLE.

Cardiovascular Risk in Psoriasis

Patients with psoriasis have CV risk independent of traditional risk factors, and that risk is greater with more severe psoriasis. Armstrong et al. reported that patients with severe psoriasis had an increased risk of cardiovascular disease compared to those with mild-to-moderate psoriasis, but that the odds of hypertension and dyslipidemia were not significantly different between the two groups.[48] Gelfand et al. found that psoriasis conferred a risk of myocardial infarction (MI) that increases with the severity of psoriasis, independent of traditional risk factors.[22] Mehta et al. similarly found that patients with severe psoriasis have an increased risk of cardiovascular mortality, independent of traditional cardiovascular risk factors.[23] Mahiques-Santos et al. found that coronary artery disease (CAD) was significantly associated with psoriasis, plus standard risk factors including age, sex, hypertension, diabetes mellitus, dyslipidemia, and obesity. In multivariate regression analysis, psoriasis was independently associated with CAD.[14]

Along with increased CV risk, patients with psoriasis have evidence of activation of the stem cell mobilization process in the form of increased cytokine levels. Takahashi et al. reported significantly elevated serum IL-17 levels in patients with psoriasis as compared to controls. In addition, serum levels of IL-17 correlated with disease as measured by the Psoriasis Area and Severity Index (PASI).[15] Cytokine levels including IL-17 decreased after psoriasis treatment,[15] similar to the cytokine decrease noted by Wen et al.[16] in treated SLE patients. A positive correlation between IL-17 levels and psoriasis severity (PASI) has been confirmed by other investigators[49,50] as has higher serum IL-17 in patients with psoriasis than in controls.[51] Serum IL-23 levels were also reported to be significantly higher in patients with psoriasis than in controls.[13] Kyriakou et al., however, found neither IL-17 nor IL-23 elevated in psoriasis nor a correlation between PASI and cytokine levels. The authors noted that there are multiple conflicting reports and attributed the discordant results to "heterogeneity of inclusion criteria and study populations".[52]

In short, at least some patients with psoriasis have greater-than-normal serum levels of the cytokines associated with stem cell mobilization. There is likely a positive correlation between the severity of disease and serum cytokine levels, and cytokine levels are responsive to psoriasis therapy. The correlation between cytokine levels and PASI and the responsiveness of cytokine levels to treatment suggest that a simple diagnosis of psoriasis would not guarantee elevated serum cytokine levels—perhaps accounting for the discordant results of Kyriakou et al. As in SLE patients, one would most likely identify evidence of activation of the stem cell mobilization process in patients with greater disease burden and during periods of active disease.

In summary, individuals with cytokine levels consistent with activation of the stem cell up-regulation/mobilization process have CV risk not accounted for by traditional risk factors. That risk is proportional to the severity of disease in psoriasis and SLE. These observations do suggest that activation of the stem cell mobilization process results in accelerated atherosclerosis in humans as has been noted in both *Apoe -/-* and *Abca1 -/- Abcg1-/-* mice.

Blocking stem cell up-regulation/ enhanced mobilization

If activation of the stem cell up-regulation/mobilization process accelerates atherosclerosis in humans, then blocking the process could reduce CV risk. In mice, antibody blocking of G-CSF, IL-17 or IL-23 reduces circulating stem cells, suggesting that the stem cell up-regulation/ mobilization process can be turned off.[4] Anti-IL-23 and anti-IL-17 agents including ustekinumab, secukinumab, and ixekizumab are used to treat psoriasis. Data on increased or decreased CV risk with the use of cytokine blocking is limited.

Rungapiromnan et al. reported a meta-analysis that showed no increase in adverse cardiovascular events in psoriasis patients treated with anti-cytokine agents.[53] Papp et al. reported data from 3117 patients treated for up to five years with ustekinumab and did not identify an increased risk of major adverse cardiovascular events (MACE). They did not identify a decreased risk of MACE either, but noted that,

> collectively, the reported rates of MACE across studies of biologics are lower than those reported in epidemiological studies of the general psoriasis population receiving non-biologic systemic treatments. Whether or not biologics in general, and IL-12/23 inhibitors in particular, are associated with an increased or a decreased risk of CV disease in psoriasis remains to be investigated.[54]

The Vascular Inflammation in Psoriasis - Ustekinumab Trial (VIP-U Trial) compared the effect of blocking IL-23 with ustekinumab versus placebo on vascular inflammation in

patients with moderate to severe psoriasis.[55] The authors demonstrated a decrease in the study's vascular inflammation marker (FDG-PET/CT) in treated patients, as opposed to an increase in vascular inflammation in the placebo group. This hopefully would translate to a reduced rate of atherosclerosis and fewer adverse cardiovascular events if continued for longer than the 12- week study period.

Stem cell mobilization as therapy?

If activating the stem cell up-regulation/mobilization process potentially accelerates atherosclerotic disease, then iatrogenic triggering of the process as a therapy for arterial occlusive disease may be counterproductive. Stem cells have been investigated as a means of generating new blood vessels to treat both coronary and peripheral artery occlusive disease.[17,19] Different approaches to the delivery of stem cells to target sites have been reported. One method is marrow aspiration and then re-introduction of autologous cells at target sites.[17] An alternative is to mobilize stem cells out of bone marrow via administration of G-CSF,[19] as done in bone marrow transplant donation and G-CSF monotherapy.[6] These two methods, in effect, compare the CV risk of activation of the stem cell up-regulation/mobilization process in similar patient populations.

Fadini et al., in a meta-analysis, suggested that,

> autologous cell therapy was effective in improving surrogate indexes of ischemia, subjective symptoms and hard endpoints (ulcer healing and amputation). On the contrary, G-CSF monotherapy was not associated with significant improvement in the same endpoints.[18]

G-CSF monotherapy may accelerate atherosclerosis by activating the stem cell up-regulation/mobilization process. Hill et al. reported that a five-day course of G-CSF resulted in two of 16 patients suffering serious adverse events, including a myocardial infarction (MI) following the fifth G-CSF dose and a death due to MI 17 days after treatment. The treatment resulted in no improvement in exercise duration at one month or at three months, no improvement in cardiac endpoints, and a trend towards a greater number of ischemic cardiac segments. In their discussion, Hill et al. noted reports of "myocardial infarction … in cancer patients and in healthy subjects receiving G-CSF."[19]

Katsaros et al. found that serum G-CSF levels, in patients with stable coronary artery disease, are predictive of major adverse cardiovascular events, independent from traditional cardiovascular risk factors.[7]

Conclusion

In *Apoe -/-* mice, experimental injury activates the stem cell up-regulation/mobilization process, resulting in accelerated atherosclerosis through modification of arterial plaque.[1,2] *Abca1 -/- Abcg1-/-* mice have chronic genetic activation of the stem cell up-regulation/mobilization process, with cytokines IL-17, IL-23, and G-CSF all necessary components of that process.[4] The same cytokines can be elevated in the serum of patients with SLE, psoriasis and chronic liver disease.[8,9,11,13,15,16,31–33] SLE and psoriasis are independent risk factors for cardiovascular disease,[12,14] and chronic liver disease is also associated with cardiovascular disease.[10] Activation of the stem cell mobilization process, as suggested by human serum cytokine levels, appears to accelerate atherosclerosis in humans as well as in mice.

Two observations follow. The first observation is that the rate of progression of atherosclerosis in patients with SLE, psoriasis, and liver disease could be altered by addressing the disease-triggering activation of the stem cell mobilization process. Atherosclerotic disease in these patients could be impacted, even prior to our full understanding of why atherosclerosis is accelerated by activation of the stem cell up-regulation/mobilization process. The cytokines associated with stem cell up-regulation/mobilization could be used to identify individuals at risk for accelerated atherosclerosis and to monitor the effectiveness of interventions, as has been advocated by other authors. Westerterp et al. have suggested measuring serum G-CSF,[56] but serum IL-17 or IL-23 might be alternatives. An advantage to G-CSF is that plasma G-CSF levels have been shown to predict major adverse cardiovascular events in patients with stable coronary artery disease, independently from established CV risk factors.[7]

The second observation is that, if activation of the stem cell up-regulation/mobilization mechanism does accelerate human atherosclerosis, then iatrogenic activation of that process might be reconsidered as a therapy for arterial occlusive disease. As noted above, stem cell therapies have been employed to treat arterial occlusive disease, either by direct injection of cells at target sites or by activation of the stem cell mobilization mechanism.[17–19] Regarding the CV risk seen particularly in patients with SLE and psoriasis, direct injection of cells would appear to be the preferable method of delivering stem cells to target vessels. Activation of the stem cell up-regulation/mobilization process (G-CSF administration) might worsen arterial occlusive disease by accelerating atherosclerosis.

Abbreviation list

ABCA1, ATP-Binding Cassette transporter 1; AFL, Alcoholic Fatty Liver disease; ALT, Alanine Transaminase; CAD, Coronary Artery Disease; CH, Cholesterol; CPCs, Circulating Progenitor Cells; CT, Computed Tomography; CV, Cardiovascular; G-CSF, Granulocyte Colony-Stimulating Factor; HCC, Hepatocellular Carcinoma; HCV, Hepatitis C Virus; IL-17 and IL-23, Interleukin-17 and -23; LDL, Low-Density Lipoprotein; MACE, Major Adverse Cardiovascular Events; MI, Myocardial Infarction; NAFLD, Non-Alcoholic Fatty Liver Disease; PASI, Psoriasis Area and Severity Index; SLE, Systemic Lupus Erythematosus; TG, Triglyceride; U/S, Ultrasound; VIP-U Trial, Vascular Inflammation in Psoriasis - Ustekinumab Trial.

Ethics approval and informed consent

This study did not require approval by our Institutional Review Board (Committee for Protection of Human Subjects).

Consent for publication

The consent for publication is not applicable for this article because details, images or videos relating to individual participants are not included in the manuscript.

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Author contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of this work.

Disclosure

The authors report no conflicts of interest in this work.

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